Archives of Dermatology and Syphilology

VOLUME 44 NOVEMBER 1941 NUMBER 5

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ECTODERMAL AND MESODERMAL DYSPLASIA WITH OSSEOUS INVOLVEMENT

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Occasional reports have appeared in medical literature on ectodermal defects or ectodermal dysplasias. Some of the anomalies have been of the anhidrotic type. Rarely has there been any suggestion of possible concomitant mesodermal involvement. A case of such involvement as well as of an osseous aplasia is presented here, with a discussion of the salient characteristics and unusual relations.

REPORT OF A CASE

M. E., a white woman aged 26, unmarried, an office worker, had had a disturbance of the skin since birth.

Family History.—The father, 52 years of age; the mother, 45 years of age, and two sisters, 19 and 10 years of age, were living and well. There had been no other pregnancies. There was no history of a similar condition in any known member of the family, nor was there a history of insanity, cancer, tuberculosis, congenital heart disease or epilepsy.

Past History.—The patient's health in general was good. She had had the usual diseases of childhood. Her appendix ruptured when she was about 14; it was removed and the wound drained. Complete recovery took place. A review of systems gave negative results.

Present Illness.—At birth it was noted that there was webbing of the third and fourth fingers of the right hand and of the first and second toes of the left

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Read at the Sixty-Fourth Annual Meeting of the American Dermatological Association, Inc., New Orleans, April 7, 1941.

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foot, of which the third digit was absent. As far back as she could remember the patient had tolerated heat poorly, and she "smothered," as she called it, in the hot sun. She had not observed much change in the character of the skin in recent years. She had no particular discomfort from her skin, although she burned easily on exposure to sunlight. She had never perspired much except in the axillas and on the palms.

Physical Examination.—The patient was medium sized, well nourished, feminine, intelligent and somewhat reticent. The pupils were round, regular and equal. They reacted normally. The fundi were normal. The ears were normal. The nose was slightly sunken at the bridge but otherwise normal. The vermilion border of the lips was fairly well defined. Most of the teeth were smaller than normal. The upper right premolar and molars were hypoplastic; they were not cone shaped.

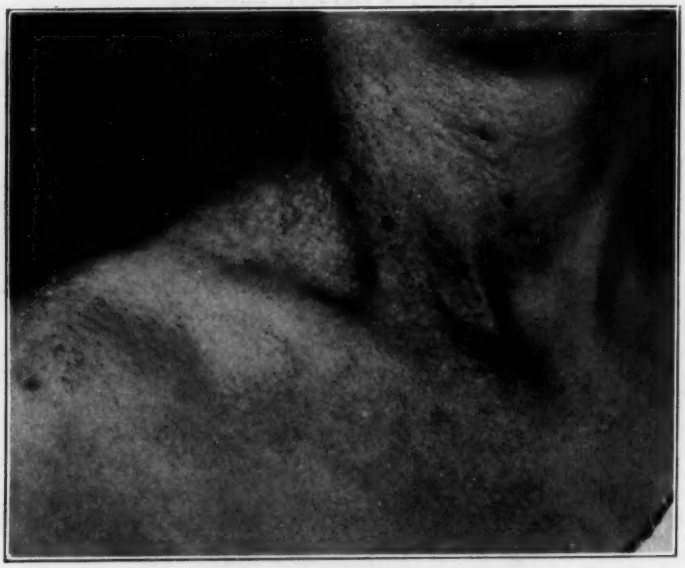

Fig. 1.—Fine atrophic areas and spots of telangiectases on the neck.

There were several gold fillings and inlays. No leukoplakia was present. The tonsils were chronically infected. There was no localized or general enlargement of lymph nodes. The breasts were virginal and fairly well developed. The lungs were clear. The heart, the abdomen, except for a scar in the right lower quadrant, and the external genitalia were normal. Pelvic and rectal examinations were not made. A neurologic survey was noncontributory.

Laboratory Examination.—The urine was normal. Examination of the blood showed leukocytosis (between 11,000 and 14,000 leukocytes); erythrocytes, 5,300,000; hemoglobin, 90 per cent, and a differential count of polymorphonuclear leukocytes 86 per cent, eosinophils 6 per cent and basophils 2 per cent. The Kline exclusion test gave a negative result. The values for blood urea nitrogen, plasma cholesterol, fasting blood sugar, serum phosphorus, serum phosphatase, plasma carbon dioxide and plasma chlorides were all within normal limits. Roentgenograms of the skull and chest were normal. A roentgenogram of the left foot showed the third toe and the metatarsal bone to be absent.

Cutaneous Examination.—There was an eruption which was most extensive on the chin extending down over the neck and on the shoulders. The skin was a delicate pale yellow, and scattered freely throughout the entire affected area there were fine, pale gray, depressed, atrophic areas, varying in size from that of a pinhead to that of a split pea. The latter were particularly extensive above the clavicles. Telangiectases were numerous on the chin and less extensive on the neck.

Fig. 2.—Linear aspect of telangiectases and pigmentation on the extremities.

The fine reticulated atrophy extended over the upper part of the chest and on the arms. Along the flanks and up toward the axillas the areas of depressed atrophy were somewhat larger, up to bean sized, and the surrounding slightly raised pale yellow skin was sharply contrasted. The process was particularly extensive on the right flank and extended posteriorly to the spine and over the

lower part of the back, on the right side more than on the left. Scattered over the entire areas just mentioned were pinhead-sized to pea-sized yellowish brown pigmented spots. Some fine telangiectases were also noted. The arms, particularly the right one and especially below the elbow, showed the same fine atrophic areas, but extending on both arms from a little below the shoulder down almost to the wrists were numerous telangiectases arranged in linear fashion. This condition was more striking on the extensor than on the flexor surface. Pigmented spots were scattered over the areas, and on the flexor surfaces of the arms there were a few slightly raised fine pale yellow papules.

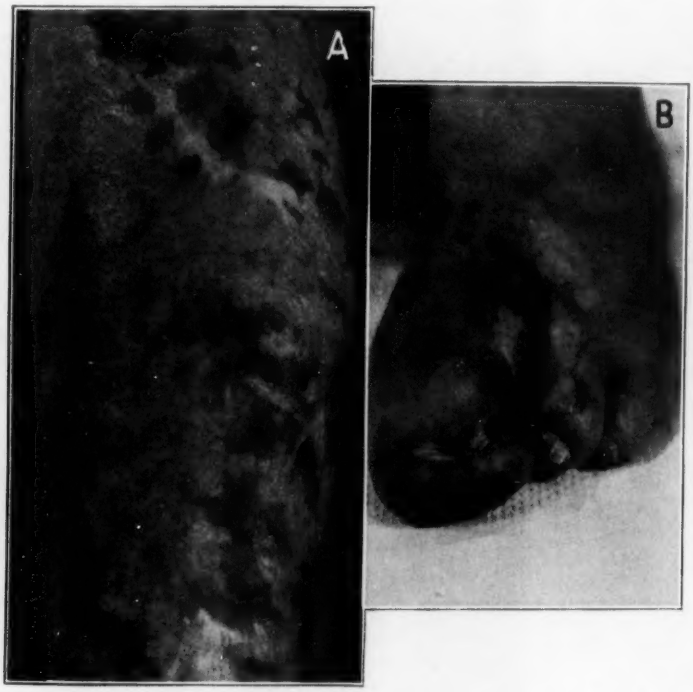

Fig. 3.—*A*, outer aspect of the left calf, showing clumps of pigmentation, telangiectases and atrophy (anetoderma). *B*, congenital absence of the third toe and complete syndactyly of the first two toes.

There was a roughly symmetric linear arrangement of pea-sized to bean-sized pigmented spots running down the thighs and legs posteriorly almost to the ankles. Telangiectases were scattered throughout the areas, especially below the knees. On the outside of the left leg from the knee almost to the ankle the skin had the appearance of anetoderma with large clumps of pigment, fine telangiectases and in a few spots underlying vessels showing up clearly through the overlying thin covering. Another anetoderma-like area was found at the crest of the right ilium, which was about twice the size of the hand and extended down onto the upper part of the thigh anteriorly. The left leg was definitely smaller than the right. Just above the left ankle were some pale yellow characters and atrophy as seen on

the neck, and this picture was also present on the skin on both sides of the cleft in the foot. The foot showed complete fusion of the first two toes and absence of the third toe and metatarsal bone.

The middle finger of the left hand showed a syndactyly and a claw finger resulting from operative intervention. The nails of the right hand showed leukonychia punctata. There were spoon nails on the first two toes of the left foot, where there was complete syndactyly. The nail of the right hallux was dystrophic. The axillary, head and pubic hair was normal except for partial absence of hair over the right side of the mons. The eyebrows and eyelashes were normal. No hair was noted on the rest of the body. The palms and soles were normal.

Course in Hospital.—Experimentally the patient was wrapped in three blankets. At the end of three hours she had a slight elevation of temperature and an increase in the respiratory rate from 18 to 22. During this time there was no sweating except in the axillas and on the palms. Two days later the procedure was repeated with the additional feature of giving the patient 1/12 grain (0.005 Gm.) of pilocarpine nitrate a few minutes before. As a result of this, she perspired a little more than she did two days previously, in the aforementioned areas. There was a rise in temperature, but less than 1 degree (F.).

Microscopic Examination.—Unfortunately the patient would not consent to the taking of specimens for biopsy from more than four areas. Consequently the description of the microscopic picture will of necessity be limited to these areas.

Section 1 was obtained from a pigmented area on the upper part of the left calf. The specimen, fixed in a solution of formaldehyde, consisted of a cigaret-paper-like, elliptic piece of skin, measuring 19 by 9 by 2 mm. The surface was mottled brown and yellowish gray. The under surface consisted of fibroadipose tissue. The skin cut with the usual resistance. The entire specimen was embedded.

The cutaneous surface was undulated and the keratinized layer normal in places and scanty in others. The epidermis varied from six to ten layers in thickness, and the rete pegs were for long stretches absent. The granules of the stratum granulosum were prominent in some regions and obscure elsewhere. Occasional normal mitoses were seen in the stratum mucosum. The epidermal pigment was prominent in parts of the stratum germinativum, while in other parts none was evident. The focal absence of corium was striking. In these regions the fat of the subcutaneous tissue lay immediately beneath the epidermis. In the papillary zone there were a few lymphocytes about the vasa. There were no hair follicles or glands in the section. Elastic tissue and Van Gieson stains showed focal absence of both elastic and collagenous tissue in the region of the corium.

Section 2 was obtained from the outer, middle portion of the left calf. The specimen, fixed in a solution of formaldehyde, was a cigaret-paper-like, elliptic piece of skin with underlying fibroadipose tissue. The specimen measured 26 by 6 by 5 mm. The surface of the skin was mottled pale gray and brownish gray. The architecture was irregularly distorted and finely granular. On section the skin was thin. The entire specimen was embedded.

The epidermis was fairly uniform in thickness, with the keratohyaline layer thin or normal, but occasionally it was detached, whether naturally or as the result of an artefact not being certain. The epidermal pigment was uniformly distributed and normal in amount. Principally in the stratum germinativum but occasionally extending to the more superficial layers were focal masses of bodies corresponding to the *corps ronds* of Darier. The corium was scanty or absent.

The elastic and the collagenous tissue were normal in some places but absent elsewhere. There were a few lymphocytes about the vasa in the region of the upper part of the corium, and here were also scattered small, elliptic cells laden with minute, brown pigment granules. No hair follicles or glandular structures were present.

Section 3 was from the right flank above the crest of the ilium, a scarlike area (possible amniotic adhesion). The specimen, fixed in a solution of formaldehyde, consisted of an elliptic piece of skin with underlying fibroadipose tissue. The specimen measured 26 by 6 by 5 mm.; the surface was brown, pale gray and

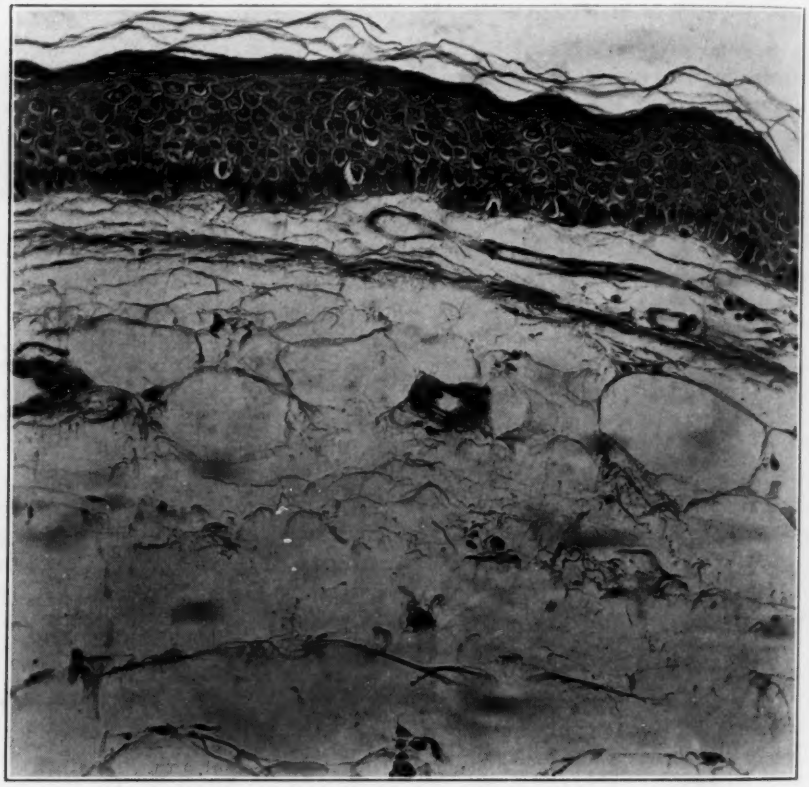

Fig. 4.—Photomicrograph showing pigmented areas of outer part of the left calf and absence of the corium with replacement by adipose tissue (× 238; hematoxylin and eosin).

irregular. The pale areas appeared to be contracted and scarlike. The skin cut with considerably increased resistance and was irregularly thickened, tough and firm. The entire specimen was embedded.

Part of the epidermis was normal and had a fairly uniform keratinized layer. Other parts showed increased thickness of the keratinized layer, generally thickened epidermis, as well as lengthened and widened rete pegs. Most parts of the corium showed increased collagenous and elastic tissue, and this formed a wide reticular zone. Much of this was densely packed together, with the upper part of the

corium well vascularized. There were components of sudoriferous and sebaceous glands and one hair shaft in this tissue. Moderate numbers of lymphocytes and occasionally a polymorphonuclear neutrophilic leukocyte were found in the papillary zone. Most of these were around blood vessels, but in some places they were disposed as moderately large foci not in relation to vessels. There were scattered small, elliptic, pigment-laden cells in the upper part of the papillary zone. The pigment was in the form of minute brown granules. These did not show the reaction for iron, and a test for melanin gave a positive reaction. At one point there was a peculiar arrangement of the cells beneath the basement membrane of

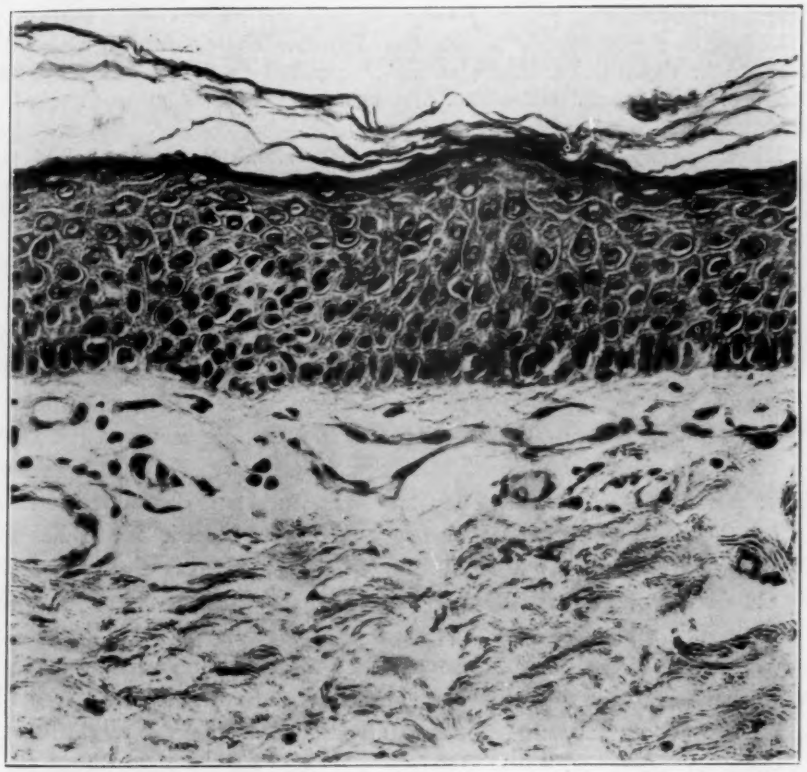

Fig. 5.—Photomicrograph showing paucity of elastic and connective tissue fibers and occasional melanin pigment cells in the upper corium. Note the absence of sebaceous and coil glands, as well as of hairs (× 342; hematoxylin and eosin).

the epidermis. Here the cells were attenuated and arranged in palisade formation radiating essentially perpendicular to the basement membrane.

Section 4 was cut from an atrophic-like area on the right flank. The specimen of skin, fixed in a solution of formaldehyde, was elliptic and measured 16 by 5 by 3 mm. The surface was undulated, irregular, mottled pale and dark gray. The skin cut with increased resistance and was moderately thickened and irregular. The entire specimen was embedded.

Parts of the epidermis showed long and wide rete pegs but a normal keratinized layer. Most of the papillae were pale, with a loose arrangement of immature connective tissue cells which had stellate outlines and large pleomorphic vesicular

nuclei. The upper part of the corium was well vascularized, and about the vasa were moderate numbers of lymphocytes, a few slightly larger, oval mononuclear cells and a few eosinophilic leukocytes. Components of sudoriferous glands were present, but there were no sebaceous glands or hair follicles. Special stains revealed a paucity of elastic and collagenous tissue in the papillary zone, but these tissues were abundant in the underlying, thick, dense reticular layer.

Summary.—A 26 year old woman with no relevant family history had a cutaneous disturbance since birth. She had never perspired much except in the axillas and on the palms. There was a disseminate type of atrophoderma with telangiectasis and pigmentation on the chin, neck, arms, trunk, anteriorly in particular, and extremities, especially the right arm and the left leg. There was anetoderma on the entire outer aspect of the left leg. There was some hypoplasia of the right upper molars and premolars. She had syndactyly of the middle fingers of the left hand and of the first two toes of the left foot. The third metacarpal bone and toe were absent.

Microscopically the ectodermal elements, hair, hair follicles, sweat and oil glands were focally absent, while the mesodermal elements, elastic and collagen fibers were usually scanty. Occasionally the entire cutis was absent. Melanin pigment was found in the upper part of the corium in some places. Bone, also a mesodermal element, was involved in this case.

COMMENT

In 1883 an American dentist, Guilford,[1] described the first case of congenital ectodermal dysplasia of the anhidrotic type. This patient, a man aged 48, though always well, was edentulous. He had almost complete absence of taste and entire absence of smell. He was hypotrichotic, had a saddle nose with prominent bony bosses over his eyes and had never perspired. It remained for another American, Goeckermann,[2] to report the sixth case, that of the first female so affected. He laid down the dicta for the abnormality and stated that in the classic form there should be congenital absence of teeth, hypotrichosis, total absence of sweat glands and almost total absence of sebaceous glands. Since then more of these cases have been reported so that the number now reaches somewhere between 40 and 50. The exact number is not essential, and it stands to reason that this by no means comprises the total number of cases in existence.

In the American literature the condition has been fully discussed and cases have been reported by MacKee and Andrews,[3] Weech,[4] Gordon and Jamieson,[5] Hill,[6] Lord and Wolfe,[7] Kerley [8] and Clauston.[9]

1. Guilford, S. H.: A Dental Anomaly, Dent. Cosmos **25**:113-118, 1883.

2. Goeckermann, W. H.: Congenital Ectodermal Defect: Report of a Case, Arch. Dermat. & Syph. **1**:396-412 (April) 1920.

3. MacKee, G. M., and Andrews, G.: Congenital Ectodermal Defect, Arch. Dermat. & Syph. **10**:673-701 (Dec.) 1924.

4. Weech, A. A.: Hereditary Ectodermal Dysplasia (Congenital Ectodermal Defect): A Report of Two Cases, Am. J. Dis. Child. **37**:766-790 (April) 1929.

5. Gordon, W., and Jamieson, R. C.: Hereditary Ectodermal Dysplasia of Anhidrotic Type, Ann. Int. Med. **5**:358-370, 1931.

(Footnotes continued on next page)

The patient described by MacKee and Andrews, a boy aged 14, had congenital absence of sweat glands with intolerance to heat, absence of pilosebaceous apparatus over most of the body, advanced dental aplasia, saddle nose, prominent supraorbital ridges, thick protrusive lips, thin hair and smooth, dry skin. He also had deformed ears, a mongolian facies, dystrophy of the nails and papular facial lesions. Much has been written in the English literature, but for our purposes the article by Weber [10] and the discussion by Cockayne [11] of inherited abnormalities of the skin are comprehensive. While much is found in foreign literature, the entire subject has been reviewed and discussed at length in the articles by Siemens [12] and Steiner [13] in Jadassohn's handbook.

There is apparently a unanimity of opinion that this condition is a rare sex-linked recessive (i. e., transmitted by females and appearing in some of the male members) inherited dermatosis characterized in the main by a varying absence of teeth, hair and sweat and oil glands. In addition, the patients may have saddle nose with or without ozena, bulging of the supraorbital prominences, thick protrusive lips, due to hypertrophy of the gums, dystrophy of the nails and intolerance to heat. Clauston expressed the opinion that some patients with this condition unrecognized die in early childhood from the inability to stand changes in temperature. In some there is also a lowered sense of taste and of smell. The term that seems to be now generally accepted for this condition is "the anhidrotic type of congenital ectodermal dysplasia." We prefer the term dysplasia rather than defect. Dysplasia is defined as "an abnormality in development."

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6. Hill, A. M.: Hereditary Ectodermal Dysplasia of the Anhidrotic Type: Report of a Case with the Results of Biopsy, Arch. Dermat. & Syph. **28**:66-72 (July) 1933.

7. Lord, L. W., and Wolfe, W. D.: Hereditary Ectodermal Dysplasia of the Anhidrotic Type (Congenital Ectodermal Defect), Arch. Dermat. & Syph. **38**:893-901 (Dec.) 1938.

8. Kerley, C. G.: Hereditary Ectodermal Dysplasia (Weech) in a Boy Fifteen Months of Age, Arch. Pediat. **47**:639-642, 1939.

9. Clauston, H. R.: The Major Forms of Hereditary Ectodermal Dysplasia (with an Autopsy on the Anhidrotic Type), Canad. M. A. J. **40**:1-7, 1939.

10. Weber, F. P.: A Note on Combined Congenital Ectodermal Defects, Brit. J. Child. Dis. **26**:270-275, 1929.

11. Cockayne, H. A.: Inherited Abnormalities of the Skin and Its Appendages, London, Oxford University Press, 1933.

12. Siemens, H. W.: Die Vererbung in der Ätiologie der Hautkrankheiten, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929, vol. 3, pp. 1-162.

13. Steiner, K.: Angeborene Anomalien der Haut, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 4, pt. 1, pp. 1-127.

While the classic form of the disease satisfies the requirements as given, it must be admitted that there are now quite a few cases reported in which the condition in females from the standpoint of symptoms satisfied the aforementioned requirements. Hence Siemens expressed the opinion that there must also be forms of this disease of other causation. To put it in another way, Cockayne would classify such forms as an incomplete dominant, sparing the females or affecting them as a rule less severely.

There is also a further group of persons, with an even division of the sexes, in which there may be a variety of gradations of the aforementioned symptom complex, perhaps patients with intact sweat glands but with some of the other components of this disease, e. g., a dystrophy of the nails and possibly a lessened number of teeth, widely separated and of the conical type described as characteristic of the process. Again a patient may be encountered having a partial hypotrichosis, and perhaps anonychia. Many different dysplastic combinations have been described, and in some instances they have been seen in successive generations. Cockayne stated that the disease is probably an incomplete dominant in its characters. While universal aplasias or hypoplasias of the entire skin are not known, yet there may be an aplasia of a single component, e. g., albinism, congenital anonychia or congenital hypotrichosis.

On the other hand, localized areas of aplasia or hypoplasia of the skin not only are conceivable but have been reported. The patient described by Greene and Abramson [14] had an area of alopecia on the back of the head, partial absence of the eyebrows, dystrophy of the nails, irregularly formed and widely spaced teeth and a flat broad nose. There was no anhidrosis. Stiemer classified the case as one of a "combined ectodermal dysplasia." Many other illustrations might be furnished, such as the case of Hell,[15] in which there were four distinct sharply circumscribed areas of atrophy on the body, some of them resembling scleroderma somewhat and some idiopathic atrophy, the veins shimmering through a thin, cigaret-paper-like skin.

Sharply localized areas of aplasia are not uncommon. Terruhn [16] in 1930 reviewed 105 cases of this condition, adding some of his own. He pointed out that in most of the cases the condition occurred on the head, especially along the line of the fontanels. It may occur on other

14. Greene, D., and Abramson, H.: Hereditary Ectodermal Dysplasia, Am. J. Dis. Child. **42**:1401-1406 (Dec.) 1931; abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **40**:807-808, 1932.

15. Hell, J.: Angeborene bezirksweise auftretende Hautatrophie, Dermat. Ztschr. **41**:361-364, 1924.

16. Terruhn, E.: Ueber die Entstehung amniogener Hautdefekte während der Schwangerschaft, Arch. f. Gynäk. **140**:428-460, 1930.

parts of the body. In the case reported by Sutton [17] these areas occurred along the flanks. In a case reported by Abt [18] they were present as open wounds over both knees, which soon healed. He stated the opinion that the term congenital atrophy is a faulty one for this condition, as it implies a degeneration of formed tissue, and that is not present.

The patient described by Dowler [19] had localized aplasias of the scalp and subcutaneous areas on the trunk and legs. When seen thirteen days later most of them had healed. Dubreuilh and Petges [20] have discussed the relation of some of these areas on the scalp to nevi. These localized aplasias may be of any shape and involve ectoderm only or even true skin down to the periosteum, and in certain cases the bone also has been affected. This will be discussed further.

STRUCTURAL INVOLVEMENT IN INHERITED ABNORMALITIES OF THE SKIN

The terms ectodermal defects, ectodermal dysplasias, hypoplasias and aplasias are used freely in discussing this group of unusual conditions. It is true that in many cases the ectodermal structures alone are involved. This would include the epidermis, the hair, the nails, the epithelium of the mucous membrane, the enamel of the teeth, the sweat and oil glands, the hair follicles and even the adrenal glands. It is these structures that are involved in the anhidrotic type of ectodermal dysplasia. The dentine of the teeth, however, is of mesodermal origin, and various writers have pointed out that in certain instances mesodermal structures may have been involved.

The case under discussion is particularly instructive and most uncommon because of the extensive involvement of ectodermal elements, such as the enamel of the teeth, sebaceous and coil glands, hair follicles and nails. Conversely, there is even as great a mesodermal involvement in the form of absence of elastic and collagen fibers, in fact, of the entire cutis, as in some places the subcutis comes right up to the epidermis; finally, there is also involvement of the bone.

INVOLVEMENT OF OSSEOUS STRUCTURES

There have been a few cases of these dysplasias with involvement of bony structures. Walz,[21] in discussing the subject and in view of

17. Sutton, R. L., Jr.: Congenital Defect of the Skin of the New Born, Arch. Dermat. & Syph. **31**:855-857 (June) 1935.

18. Abt, I. A.: Congenital Skin Defects, Am. J. Dis. Child. **14**:114 (Aug.) 1917.

19. Dowler, V. B.: Congenital Defect of the Skin in a Newborn Infant, Am. J. Dis. Child. **44**:1279-1284 (Dec.) 1932.

20. Dubreuilh, W., and Petges, G.: Des alopécies congénitales circonscrites, Ann. de dermat. et syph. **9**:257-280, 1908.

21. Walz, W.: Zur Kenntnis und Ätiologie der kongenitalen Hautdefekte am Scheitel Neugeborenen, Monatschr. f. Geburtsh. u. Gynäk. **65**:167-178, 1924.

accompanying developmental deformities, would classify congenital cutaneous defects on the head under the headings of acrania, hemicrania, encephalocele and congenital defects. In one of his cases there was a defect with its base right on the periosteum.

Firth [22] reported a group of cases in which there was a congenital absence of the patella along with dystrophy of the nails. He pointed out that these were not sporadic cases of absence of the patellas, which are by no means rare, but rather cases of a true hereditary process. The point was also made that in certain of these cases vestiges of patellas were found. Turner [23] also observed this familial condition and added that he found thickenings and processes on different bones, especially near the joints, with consequent inability of the arms to straighten out.

Baisch [24] described a patient, a 2½ year old girl, who had a familial syndactyly and polydactyly and a hypoplasia of the interphalangeal joints of the fingers and toes. The patient had almost a total anonychia and was partially edentulous.

Weber [10] discussed the literature of the last fifty years in regard to the combined ectodermal defects in which there have been an aplasia or a hypoplasia of the patellas, anomalies of the finger and knee joints and defects of the clavicles.

Thannhauser [25] described a man aged 23 with a true recessive sex-linked anhidrotic ectodermal dysplasia, who had never perspired until the age of 16. He showed signs of adrenal insufficiency and had a blood pressure of about 90 systolic and 60 diastolic. The patient also had exostoses over the inner table of the skull. Thannhauser stated that in all true cases of this type there are these deformities of the cranial bones. He also tried to show by his case that the "saddle nose" supposed to be characteristic of this disease is not a defect of the nasal bone but rather a bulging of the frontal prominences and that the depression at the base of the nose results from a narrowing of the sinuses. This might explain in part the deformity seen in some of the cases, but hardly a true ozena.

A case of even more extensive involvement of the bones was observed by Friedman.[26] In this classic case of the disease there were,

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22. Firth, A. C. D.: Hereditary Absence of the Patellae and Deformity of the Nails, Brit. J. Child. Dis. **9**:305-311, 1912.

23. Turner, J. W.: An Hereditary Arthrodysplasia Associated with Hereditary Dystrophy of the Nails, J. A. M. A. **100**:882-884 (March 25) 1933.

24. Baisch, A.: Anonychia congenita, kombiniert mit Polydaktylie und verzogertem abnormen Zahndurchbruch, Deutsche Ztschr. f. Chir. **232**:450-457, 1931.

25. Thannhauser, S. J.: Hereditary Ectodermal Dysplasia of the Anhidrotic Type, J. A. M. A. **106**:908-910 (March 14) 1936.

26. Friedman, R.: Hereditary Ectodermal Dysplasia of Anhidrotic Type, Urol. & Cutan. Rev. **44**:464-468, 1940.

in addition, a defect of the fifth lumbar vertebra (spina bifida) and of the sacrum and absence of a coccygeal segment. Cockayne reported that Deutsch reported a case in which there was a cleft hand. The original report, unfortunately, is not available.

In some ways the skin of our patient resembled that of the 14 year old girl described by Liebermann.[27] This child had a dysplasia of the teeth with microdontism and hypertrophy of the gums. Distributed freely over the body, with the exception of the face, neck, breasts, palms and soles, was an eruption made up of lesions varying in size from that of a pea to that of a 15 kopeck piece. The arrangement in some places was annular, in others, particularly on the extremities, linear and corresponding to the distribution of nerves. The color varied from a reddish blue to reddish brown on the upper extremities and was reddish violet on the lower ones. Many of the lesions were atrophic in appearance, especially in the linear portions on the arms and thighs. And in such areas telangiectases and pigmentation were noticeable. The patient also had numerous small scattered areas of atrophy distributed widely over the body. The degree of the atrophy varied. The author felt that the entire process was due to trophic intrauterine disturbances. The patient did differ somewhat from ours in having fine wartlike hypertrophies in the axillary and popliteal zones, while around the anal orifice there were real vegetations. Microscopic examination revealed atrophy or lessening of the elastic tissue and poorly developed sweat and oil glands. The author spoke of a lipomatosis of the cutis. The query arises whether his photomicrograph does not show the same picture that was seen in many of ours, i. e., complete absence of the cutis vera, with the subcutaneous layer coming right up to the epidermis. Professor Davidovsky expressed the opinion that "this congenital disease belongs to some deviation in the development of the ectoderm and the mesoderm and is to be regarded as a hypoplasia cutis congenitalis diffusa."

ETIOLOGY

We have already discussed the modes of inheritance seen in this disease. A few other factors should be pointed out. Weech suggested that the various ectodermal anomalies may arise as the result of a genetic mutation which occurs not by accident but as the occasional expression of a suppressed tendency to change, inherent in the make-up of the genes themselves. The glands of internal secretion may play a role, and some authors stress the selective action of the thyroid gland on ectodermal structure. With the localized aplasias, undoubtedly amniotic bands and adhesions are an important factor, especially with

27. Liebermann, S.: Atrophoderma linearis maculosa et papillomatosis congenitalis, Acta dermat.-venereol. **16**:476-484, 1935.

the lesions on the head. Kehrer [28] also stated that the congenital defects of the skull may be due to Simonart's threads or to Ahlfeld's amniotic bands. In the case reported by him there was a defect, deep, well defined, irregular, extending right down to the meninges, with absence of bone.

There may be multiple lesions, but most often there is only one. Occasionally there are symmetric lesions, as in the cases of Sutton and Abt. Other than the head, the abdomen and back seem to be most often involved, and in rare cases the extremities. Even the localized type may be familial, as witness a case reported by Kovacs.[29] Over the fontanel of a newborn child there was a nickel-sized irregular spot looking as if it had been curetted out. The base was red and rough. In a few days the area dried up, and it was epithelized in twelve days. The author stated that two of nine sisters of the father had the same defect. In the cases reported by Loewy [30] (the patients were identical twins) there was a keloid-like area of the midline on the back of the head. In the report of Burger [31] a mother and daughter had like areas on the vertex of the head. Graff [32] reported that both a patient and the father had a defect on the scalp.

Baisch [24] stated that the combination of pathologic anlage of inheritance of the ectoderm, in the form of defects of the nails and teeth, with that of the mesoderm, in the form of skeletal defects, seems to be characteristic of many developmental malformations.

OTHER DEVELOPMENTAL DISTURBANCES SEEN IN ECTODERMAL DYSPLASIAS

This brings up the frequency of other malformations seen in connection with these conditions. Harelip and cleft palate are not infrequent complications. The patient described by MacKee and Andrews, as well as others, had satyr ears. Syndactyly is seen, as in our case, and polydactyly may occur. Epispadias and hypospadias and absence of mammary glands are among other malformations. Christ [33] has carefully reviewed the entire subject, laying especial emphasis on ocular

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28. Kehrer: Ueber kongenitale Defekte am Schädel infolge amniotischer Verwachsungen, Monatschr. f. Geburtsh. u. Gynäk. **31**:183-197, 1910.

29. Kovacs, F.: Aplasia cutis congenita, Zentralbl. f. Haut- u. Geschlechtskr. **27**:424, 1928.

30. Loewy, E.: Kongenitale Hautdefekte und Keloide bei eineiigen Zwillingen, Dermat. Wchnschr. **79**:1660-1662, 1924.

31. Burger, K.: Kongenitaler Hautdefekte am Scheitel eines Neugeborener, Monatschr. f. Geburtsh. u. Gynäk. **70**:201-203, 1925.

32. Graff, E.: Beitrag zur Kenntnis der Aplasia cutis congenita, Zentralbl. f. Gynäk. **45**:705-706, 1921.

33. Christ, J.: Ueber die Korrelationen der kongenitalen Defekte des Ektoderms untereinander, mit besonderer Berücksichtigung ihrer Beziehungen zum Auge, Zentralbl. f. Haut- u. Geschlechtskr. **40**:1-21, 1932.

complications. He mentioned small or undescended testes. There may be excess formation, e. g., a large penis in a 3 year old child, leukoplakia or pigmentary disturbances. The large penis suggests a possible adrenal involvement. In the eyes the lens may be absent. Cataracts occur and nystagmus is seen in albinos. Hypoplasia of the teeth may be concomitant. The iris may be absent; there may be a luxation of the lens, or bulbus atrophy may occur. Microphthalmia has also been seen.

SUMMARY

We have described a 26 year old woman, with no pertinent family history, who had a disseminated atrophoderma of the chin, neck and trunk and in linear arrangement on the arms and legs, accompanied with localized pigmentation and telangiectases.

Microscopically, from an ectodermal standpoint of development, the areas showed partial to complete absence of sweat glands, oil glands and hair papillae and dystrophy of some nails and teeth. Mesodermal elements involved were collagen and elastic tissue fibers, which were absent, as well as bone. She had a congenital absence of the third toe and metatarsal bone of the left foot. There were also syndactyly of the last two fingers of the right hand and an even more nearly perfect fusion of the first two digits of the left foot.

The patient is presented because the condition is a unique example of combined ectodermal and mesodermal dysplasia of an incomplete dominant type.

ABSTRACT OF DISCUSSION

Dr. Henry N. Niles, New York: I was particularly interested in this paper because recently I have been treating a patient with an advanced form of epidermolysis bullosa hereditaria who also showed syndactyly and some osteoporotic changes in both feet and hands. There was severe destruction of the bones of both feet, particularly of the right. Surprisingly, in the roentgenogram there is not as much change in the bones as one would expect, but the changes in the skin from frequent trauma, bullous formation and scarring caused the skin over the digits to fuse and bring the bones together. Probably in this case the changes in the bone are due to disuse. There were bullae present on the front of the ankle and typical bullous lesions on the elbows. There were also bullae and scarring in the supraclavicular region. The boy also had definite defects in his teeth and hard palate. The Wassermann reaction of the blood was negative. A paternal uncle had the same condition, and two siblings had died at the age of a few weeks with similar lesions.

This case is a typical one of this disease in the advanced stages. In addition to the severe changes, the bullous formation and the syndactyly, this patient shows epithelial cysts on the ears, milium-like bodies, which have been described as typical of this condition.

Dr. William H. Goeckermann, Los Angeles: At the time I reported my case I thought that I had a rather distinctive developmental ectodermal anomaly, and in a way I think so now. In looking over the reports of other cases that

have appeared in the literature since then, it is striking to see how often that particular anomaly is characteristically reproduced.

Dr. Cole has emphasized the fact that the ectodermal anomalies may vary greatly. On the basis of my further observations, due to my interest in this particular subject, I fully subscribe to this. One is struck by the fact that the pictures are so varied. The temptation is great, when one encounters a rather interesting case, to coin some new dermatologic term. I think these conditions are often, in their partial development at least, mistaken for some other diseases that do not belong to this particular group.

When I was particularly interested in the case that I reported, I made a detailed study of embryology, much more than I had ever studied in medical school, merely to see whether I could get any clue as to when an injury might occur to the fetus or to the ovum. I found nothing at that time that gave me any suggestion as to what might be happening. About two years after my paper had been published, I received a communication from a physician in India who said that there were certain small areas in India in which this type of ectodermal defect was rather common. In his opinion, it was the result of intermarriage among persons living in that restricted area, which was a common practice. Since then I have thought that the anomaly was probably gene-bound and that one could not say there was any particular injury in those persons, except that the ancestry was probably defective.

Dr. George M. MacKee, New York: The patient that Dr. Andrews and I described some years ago was entirely different from the one reported on in this paper, in that the deformities of our patient were limited entirely to the ectoderm. As far as I can recall, the mesoderm was not involved. We also, as these authors have done, studied our patient from the standpoint of when the injury or the cause of the condition occurred. We could find nothing in the family or about the patient that was of any help. In our patient the collagen was intact and the elastic fibers were intact. There was no atrophy of the skin. There was, however, a complete absence of the cutaneous appendages. We made several histologic examinations of specimens from various parts of the body but were never able to find any appendages. There was never any sweating in any part of the body. In order to be comfortable in hot weather, the patient had to keep himself wet or stay in the cellar. I have encountered a number of similar cases since then and have read a number of reports in the literature.

I think that the authors are correct in saying that their case is unique. I have never seen such combined involvement or lack of development of the ectoderm and the mesoderm in the same patient, nor have I found any such case described in the literature.

Dr. Martin F. Engman Jr., St. Louis: I think the authors have given the proper conception of this disease, in that it combines a number of ectodermal defects which might differ in some small, probably unimportant, points.

I studied two brothers who had a congenital ectodermal defect (Engman, M. F.: Congenital Atrophy of the Skin with Reticular Pigmentation, *J. A. M. A.* **105**: 1252-1256 [Oct. 19] 1935). This condition was different clinically from the types that have been mentioned here. There were anomalies of pigmentation all over the body, a reticular kind of pigmentation, definite atrophy of the skin and sparse hair; teeth had been present but degenerated early in life. The nails disappeared early. The two brothers varied in degree of involvement. One of the brothers died recently of carcinoma of the esophagus. The mesoderm was not involved, but I believe these cases should be grouped with the cases described by these authors.

ACANTHOSIS NIGRICANS

ITS OCCURRENCE IN ASSOCIATION WITH GASTRIC CARCINOMA IN A SEVENTEEN YEAR OLD GIRL

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Acanthosis nigricans, a striking pigmentary disorder of the skin, has been the subject of numerous reports and reviews [1] since its first independent descriptions by Pollitzer and Janovsky, in 1890. There are over 260 cases on record, and it is undoubtedly true that a number of cases have been overlooked, particularly ones in which the condition is associated with a malignant growth, the significance of which overshadows the changes in the skin. The disease is characterized clinically by hyperpigmented patches varying from yellow to black, symmetrically distributed in the natural folds of the skin. There is exaggeration of the normal cutaneous markings with hyperkeratosis and verrucous and papillomatous changes.

Classification of the disease has been based on the age of the patient. The juvenile or benign type occurs in persons under 20 years of age and is rarely associated with malignant disease. Although the cause of acanthosis nigricans remains obscure, it has been reported in association with a number of conditions affecting directly or indirectly the chromaffin

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Read at the Sixty-Fourth Annual Meeting of the American Dermatological Association, Inc., New Orleans, April 8, 1941.

1. (*a*) Pollitzer, S.: Acanthosis Nigricans: A Symptom of a Disorder of the Abdominal Sympathetic, J. A. M. A. **53**:1369 (Oct. 23) 1909. (*b*) Wise, F.: Acanthosis Nigricans Following Decapsulation of Kidneys: Case Report, Discussion and Review of Literature, J. Cutan. Dis. **36**:35 (Jan.) 1918. (*c*) Moncorps, C., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, pt. 2, pp. 372-402. (*d*) Knowles, F. C.; Sidlick, D. M., and Ludy, J. B.: Acanthosis Nigricans: Adult and Juvenile Types, Arch. Dermat. & Syph. **19**:391 (March) 1929. (*e*) Goodman, H., and Barthel, E. A.: Acanthosis Nigricans Juvenilis: Review of the Recent Literature and Report of a Case, Urol. & Cutan. Rev. **39**:487 (July) 1935.

and sympathetic systems.[2] Among the factors supposedly related to the cause are metabolic disturbances, toxins, endocrine diseases, inflammatory and traumatic conditions of the stomach and chromaffin system, congenital anomalies, hereditary factors, tuberculosis and syphilis. The cutaneous lesions of the juvenile type are persistent, but the prognosis for life is good.

The adult, or malignant, type, usually occurring in persons over 20 years of age, is the commoner form of the disease. Mukai,[3] in an analysis of 218 cases, found carcinoma in 94, or 58 per cent, of the patients over 21 years of age and in 80 per cent of patients over 40 years of age.

Histologically, both types present the same characteristic picture. The changes in the skin, according to Montgomery and O'Leary,[4] are: relative and absolute hyperkeratosis; decided irregular acanthosis with adjacent areas of atrophy of the malphigian layer; elongated, narrow, papillary bodies; dense melanotic pigmentation of the basal cells of the epidermis; a few chromatophores laden with pigment, which are chiefly limited to the papillary bodies, and, usually, absence of inflammatory reaction in the cutis.

The following case is reported in detail because of several features significant from the standpoint of differential diagnosis and because, as far as can be determined, the patient was one of the youngest on record with the adult or malignant type of acanthosis nigricans.

REPORT OF A CASE

History.—A 17 year old white girl, unmarried, was admitted to the dermatologic service of the University of Virginia Hospital on April 25, 1940, complaining of darkening of the skin of six months' duration, weakness of six weeks' duration and headache for one week. Three years before admission the patient was kept out of school for what she termed a "nervous breakdown." Several months later, when she applied for employment, the Wassermann reaction of the blood was found to be positive. A diagnosis of syphilis was made, and continuous, uninterrupted antisyphilitic therapy was instituted in the form of alternating courses of an arsenical and a bismuth preparation. The last treatment was given in January 1940. Meanwhile, in November 1939 the patient for three weeks had an almost continuous sharp abdominal pain, more severe in one particular

2. (*a*) Masson, J. C., and Montgomery, H.: Relationship of Acanthosis Nigricans to Abdominal Malignancy, Am. J. Obst. & Gynec. **32**:717 (Oct.) 1936. (*b*) Wieder, L. M.: Acanthosis Nigricans: Juvenile Type, J. A. M. A. **87**:1964 (Dec. 11) 1926. (*c*) Curth, H. O.: Benign Type of Acanthosis Nigricans: Etiology, Arch. Dermat. & Syph. **34**:353 (Sept.) 1936. (*d*) Goodman and Barthel.[1e]

3. Mukai, T.: Acanthosis Nigricans, Acta dermat. **14**:460 (Nov.) 1929.

4. Montgomery, H., and O'Leary, P. A.: Pigmentation of the Skin in Addison's Disease, Acanthosis Nigricans and Hemochromatosis, Arch. Dermat. & Syph. **21**:970 (June) 1930.

point in the midepigastrium. She stated that she vomited when she became hungry but that she could take food and retain it. A week after the onset of the pain small warty growths began developing on her hands. At first these were white, and in the course of several weeks they gradually darkened to various shades of grayish black. In January 1940 a number of warts on her arms disappeared; however, those on her hands remained, and new ones appeared on the lower extremities. In the first part of February her lips and eyelids became nodular. In the latter part of March, at which time she had an illness diagnosed as pneumonia, she noticed a mass in the midepigastrium "which developed during two days, became sore, remained for a week and then seemed to disappear." About April 20 dull, constant, frontal and occipital headaches developed, which became so severe that she was sent to the hospital.

The history revealed that at the age of 12 years she had swelling of the ankles, attributed to "leakage of the heart"; this condition improved with rest, but she had occasional recurrence of the swelling. The menstrual periods had always been irregular, occurring every two or three months; flow was scanty and accompanied by severe cramping pain. The last period had occurred several weeks prior to admission.

For the two years previous to admission the patient was frequently exposed to a family known to have active tuberculosis. Her family history revealed no malignant disease. In 1930, when she was 7 years old, her father had a penile lesion with secondary eruption, diagnosed as syphilis and treated as such; in 1938 the mother was found to have a strongly positive Wassermann reaction. Absence of evidence of congenital syphilis and the family history led to the conclusion that the patient suffered from acquired syphilis of childhood.

Physical Examination.—The temperature, pulse and respirations were normal. The patient was pale, poorly developed and poorly nourished and appeared listless and tired, but in no particular distress. The skin of most of the body presented various degrees of black and gray discoloration, particularly intense in the axillas and in the cubital fossae but present also on the soles, on the toes, around the umbilicus, on the flank and in the perineal region. In the areas of deepest pigmentation the skin was thickened and velvety. The areolas and nipples were covered with dense, membranous, hyperkeratotic plaques, which were deeply fissured. The eyelids were nodular, with a rough serration of their margins. The lips were granulomatous, with a considerable overgrowth of tissue, fissuring, some bleeding and crusting; otherwise the mucous membranes were clear. On the dorsa of the hands, on the lower portions of the forearms and on the corresponding areas of the lower extremities were small round blackish gray verrucous lesions, 1 to 5 mm. in diameter. There was a generalized thick hyperkeratosis of the palms. All of the hair, particularly that of the eyebrows and scalp, was dry and thin with patchy areas of alopecia. The finger nails and the toe nails were normal. A loud, rough systolic apical murmur was heard over the entire precordium, and the aortic second sound was accentuated. The blood pressure was 110 systolic and 60 diastolic in both arms. The examination of the abdomen was not entirely satisfactory because of tenderness; however, there was thought to be a mass in the midepigastrium. The external genitalia were normal, and the introitus was virginal.

Laboratory Observations.—The hemoglobin amounted to 7.5 Gm. per hundred cubic centimeters of blood. The red blood cells numbered 2,800,000 and the white blood cells 7,800, with a normal differential count. The urine was normal;

no melanin was found. The Wassermann reaction of the blood was repeatedly anticomplementary; the Kahn reaction was weakly positive, and the Kline reaction was strongly positive. The urea amounted to 22 mg. and the chlorides to 605 mg. per hundred cubic centimeters of blood plasma. The carbon dioxide–combining power was 56.8 volumes per cent. The plasma amylase was equivalent to 17.5 mg. of starch per hundred cubic centimeters (70 mg. by the Somogyi method). The icterus index was 7. Analysis of the gastric contents showed no free hydrochloric acid and 26 degrees total acid; tests for lactic acid and for occult blood gave negative results. The stools were essentially normal

Fig. 1.—Axilla of patient with acanthosis nigricans, showing pigmentation and velvety thickening of the skin.

except for giving a weakly positive reaction for occult blood (benzidine tests). A tuberculin test, with 0.1 cc. of a 1:1,000 dilution of old tuberculin, elicited a negative reaction. The reaction to a test for adrenal insufficiency, as standardized by Cutler, Power and Wilder,[5] was well within the limits of normal, with 18 mg. of chloride ion per hundred cubic centimeters of urine obtained on the specified routine. Tests for arsenic in the blood gave negative results. There was 0.004 mg. of arsenic per gram of hair. A 25 mg. piece of unpigmented skin was arsenic free (negative), and a 175 mg. section of pigmented skin contained only a trace of arsenic (less than 0.001 mg.). Tests for bismuth on the same sections gave negative results.

A roentgenogram of the lungs was normal. A series of gastrointestinal roentgenograms revealed a large filling defect in the stomach, with immobilization, though apparently without stasis. An orthodiagram showed a slightly enlarged heart with a moderately prominent left auricle; the aorta was small. An electrocardiogram showed abnormalities in the T wave which were thought to indicate myocardial damage.

Course in the Hospital.—Since the patient was in such poor general condition, she was given blood transfusions and intramuscular injections of a liver extract. An oxycholesterol-petrolatum ointment (aquaphor) was applied to the lips. Her condition improved remarkably with this regimen, although the granulations on her lips continued to become more prominent. On reexamination after decrease in abdominal tenderness, a definite, irregular, fixed mass, measuring 4 by 5 cm., could be palpated in the midepigastrium.

The patient was transferred to the surgical service, and on May 17, 1940 laparotomy was performed with the patient under spinal anesthesia. Immediately the abdomen was entered a tumor, thought to represent a large carcinoma, was found in the omentum firmly attached to the abdominal wall just above the umbilicus. The entire lesser curvature of the stomach was involved in a mass which spread along the gastrohepatic ligament into the retroperitoneal tissue in the region of the celiac plexus and along the upper pole of the left kidney. The preaortic nodes and many of the nodes along the transverse colon were markedly enlarged and firm. Specimens for histologic examination were taken from the stomach and adjacent lymph nodes, and the operation was concluded. The patient had an uneventful postoperative course and was discharged after eleven days, at which time she was strong, eating a soft diet and feeling better than on admission.

Histologic Studies.—A specimen of skin from the right axilla showed the characteristics of acanthosis nigricans. There was decided hyperkeratosis with patches of parakeratosis. An irregular acanthosis was present with many finger-like rete cones, although most of the rete layer was relatively thin. Pigmentation in the granular layer was striking and was increased in the basal layer. The few long, narrow papillary bodies contained occasional pigment-laden chromatophores. The only change in the cutis was slight perivascular infiltration with lymphocytes.

Examination of a verrucous lesion from the left arm could not have established a diagnosis; however, by comparison with the preceding section it was observed that the same essential processes were present.

Although at operation the gastric mucosa was not violated, a section from the thickened wall of that viscus showed massive invasion by groups of irregular pale signet ring cells with crescentic, hyperchromic nuclei in alveolar arrangement; most of the cells contained mucoid material and were typical of colloid carcinoma. Sections of preaortic lymph nodes showed an almost complete replacement of the normal structures by metastatic carcinoma in the form of single or grouped pale cells of irregular size, containing hyperchromatic nuclei which had a high mitotic index; colloid degeneration, though present, was much less evident.

Follow-up Study.—Unfortunately, personal follow-up observation was not possible. Correspondence received on August 21, twelve weeks after the patient's discharge, stated that she was feeling well, certainly much better than when she had been in the hospital. She had no pain in her abdomen and claimed that she had an enormous appetite. She was "unable to feel the abdominal mass." Her eyelids had improved, and her lips had become normal in size but were still roughened. It was later learned that the patient died on Sept. 21, 1940.

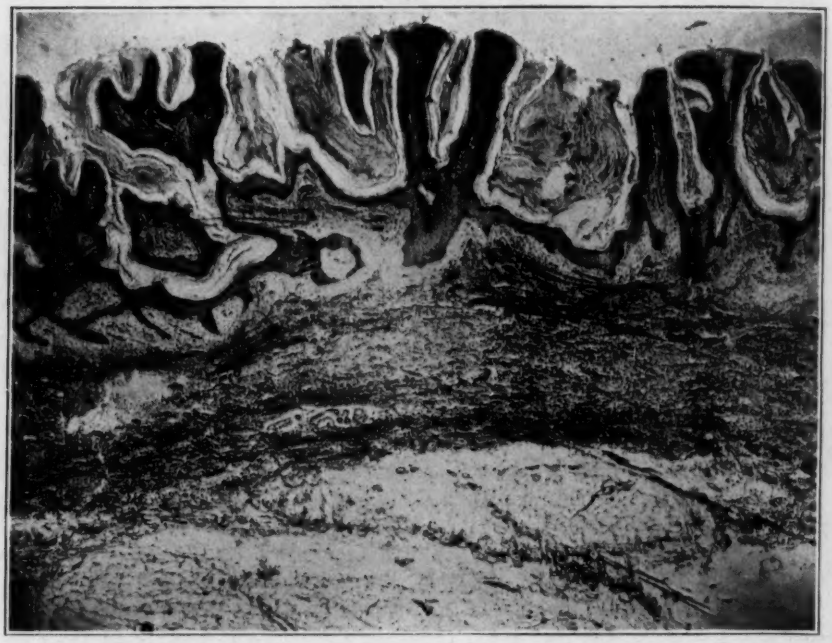

Fig. 2.—Photomicrograph of skin from the right axilla showing characteristic structure of acanthosis nigricans. The finger-like projections are particularly prominent.

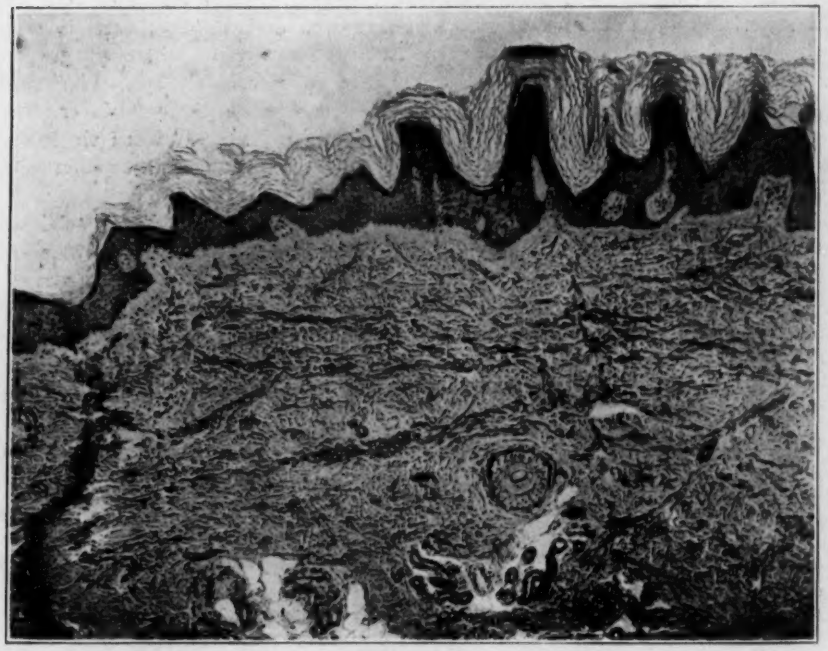

Fig. 3.—Photomicrograph of tissue from the arm showing keratosis. Note the changes leading to the flat-topped lesion.

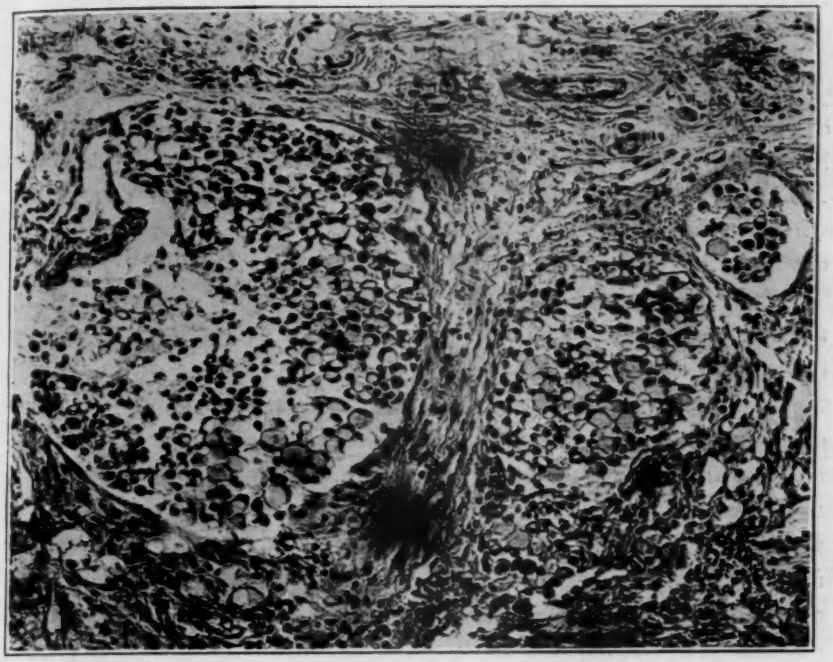

Fig. 4.—Tissue from the wall of the stomach showing the alveolar arrangement of the signet ring cells of colloid carcinoma.

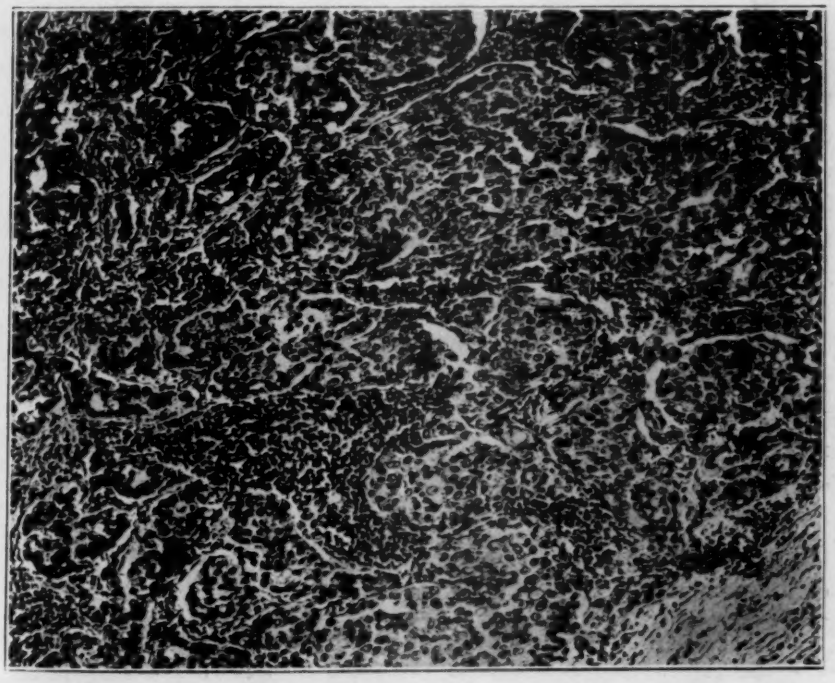

Fig. 5.—Section of a preaortic lymph node showing the almost complete replacement of the normal structure by metastatic carcinoma.

COMMENT

Acanthosis nigricans may be confused clinically with Addison's disease, hemochromatosis and arsenical pigmentation. The clinical and histologic features of these diseases have been described in detail by Montgomery and O'Leary.[4] Microscopic study of the skin of a patient with acanthosis nigricans will usually establish the diagnosis, since the cutaneous histopathologic picture is characteristic.

The subject of this report presented a problem in differential diagnosis for several reasons. The history of treatment for syphilis and the hyperkeratoses of the palms and soles, together with pigmentation of the skin, suggested arsenical pigmentation. A bismuth compound and a combination of an arsenical drug and bismuth were considered as causative factors in the widespread cutaneous discoloration. Addison's disease was suspected because of the deep pigmentation of the skin, asthenia, vomiting and history of exposure to active tuberculosis. The evidence for these diagnoses was diminished by the finding of insignificant amounts of arsenic and bismuth in sections of the pigmented skin and by the absence of hypotension and of nitrogen retention. The diagnosis of acanthosis nigricans was established by the symmetrically distributed verrucous patches on the skin, the characteristic histologic picture of the skin and the associated carcinoma of the stomach.

Cutler, Power and Wilder[5] have found diagnostic significance in the tendency of patients with Addison's disease to excrete urine containing chloride in high concentration. Under standardized conditions, patients with Addison's disease excreted between 229 and 356 mg. of chloride per hundred cubic centimeters of urine, while controls excreted from 17 to 141 mg. These authors concluded that a urinary concentration of chloride in excess of 225 mg. per hundred cubic centimeters indicated an abnormality of adrenal cortical function, whereas a concentration of less than 125 mg. probably could be accepted as evidence of normality. As far as can be determined, this procedure has not been performed previously in a case of acanthosis nigricans. In view of the widely held opinion that a close relation exists between acanthosis nigricans and Addison's disease, it may be significant that this patient excreted 18 mg. of chloride per hundred cubic centimeters of urine obtained on the specified routine. This value, which lies within the normal range, is evidence of normal function of that part of the adrenal cortex involved in electrolyte metabolism.

5. Cutler, H. H.; Power, M. H., and Wilder, R. M.: Concentrations of Chloride, Sodium, and Potassium in Urine and Blood: Their Diagnostic Significance in Adrenal Insufficency, J.A.M.A. **111**:117 (July 9) 1938.

The adult or malignant type of acanthosis nigricans has been reported in only 2 patients less than 20 years of age. Spietschka [6] reported the case of a 19 year old woman with a malignant deciduoma who experienced involution of the cutaneous changes immediately after operation and whose symptoms disappeared completely several months later. In a case reported by Halty, Correa Delgado and Volpé [7] a child born with a unilateral eruption of acanthosis nigricans showed at the age of 9 months signs of an abdominal tumor. Laparotomy, performed when the child was 2½ years of age, revealed a large malignant, inoperable growth.

Etiologic studies on acanthosis nigricans have yielded nothing conclusive. Tuberculosis, syphilis and endocrine dysfunction (as manifested by menstrual irregularity) were not of apparent etiologic significance in this case. The preponderance of clinical and pathologic evidence suggests that the disease is related to a disturbance of the chromaffin and sympathetic systems produced by one or more of a variety of conditions operating through the same mechanisms. Curth [2e] has found among the antecedents of patients with the benign type of acanthosis nigricans a high incidence of the same types of cancer (i. e., cancer of the glandular organs) that are found in patients with the malignant type. This observation suggests a genetic relation between acanthosis nigricans and certain types of cancer and a common origin for both the benign and the malignant type of the disease.

It has been made sufficiently clear in recent literature and it is illustrated by this case that no division of this disease into juvenile and adult types can be made on the basis of age. The qualifying terms benign and malignant remain useful, since the cutaneous changes are identical and cases differ only in the presence or absence of a malignant growth. The presence of cutaneous lesions of acanthosis nigricans in any patient, regardless of age, makes it necessary to undertake an exhaustive search for a concurrent malignant condition.

SUMMARY

A case of acanthosis nigricans of the malignant type associated with gastric carcinoma in a 17 year old girl is reported.

The differential diagnosis and various theories of the cause of the disease are discussed.

No abnormality of adrenal cortical function was demonstrated.

It is reemphasized that no classification of the disease may be made on the basis of age and that in any case of acanthosis nigricans, regardless of age, diligent search must be made for accompanying malignant disease.

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6. Spietschka, T.: Ueber Dystrophie papillaire et pigmentaire, Arch. f. Dermat. u. Syph. **44**:247, 1898.

7. Halty, M.; Correa Delgado, B., and Volpé, A.: Acanthosis nigricans, Rev. sud-am. de méd. et chir. **4**:189 (March) 1933; cited by Curth.[2e] (Note: The writers were unable to obtain the original paper for purposes of reference.)

ABSTRACT OF DISCUSSION

DR. PAUL A. O'LEARY, Rochester, Minn.: I persuaded several of my surgical colleagues to explore the abdomens of 3 patients who had the adult type of acanthosis nigricans. The manifestations of this disease had been present in each case but a few months. The laparotomies were performed with the idea that if malignant growth was found in the viscera its early recognition and treatment might cure the acanthosis nigricans. After a thorough clinical survey, including extensive roentgen ray studies of the gastrointestinal tract, we were unable to demonstrate any clinical evidence of abdominal cancer in any of the cases, and at operation no evidence of cancer could be found. The exploratory procedure was a thorough one, the surgeons palpating and searching all of the viscera that they could. The first patient operated on returned within about five months with a tremendous abdominal cancer, involving primarily the liver, from which he died shortly. The second patient went for a year before what apparently was a primary carcinoma of the stomach developed, and he then died within six or eight months with visceral metastasis. The third patient is still alive. It has been five or six years now since the operation was performed. The acanthosis nigricans is still present. He apparently remains in good health. In other words, in our efforts to cure acquired acanthosis nigricans by the early removal of abdominal cancer we failed.

It is striking that in an institution in which a large number of patients with abdominal cancer are encountered acanthosis nigricans is an extremely rare complication. The only deduction we have been able to draw is that we were unable to find the site of the malignant growth which subsequently developed in 2 of the 3 patients thus treated.

DR. KENDAL FROST, Los Angeles: My associates and I have had an interesting patient, a young woman with acquired masculinism. With all the early examinations no cutaneous manifestations were recorded. At the time she came under our observation—she was referred to us from the surgical service where she was being studied—she had mild changes, clinically and histopathologically, of acanthosis nigricans on the anterior axillary folds and in the groins. A tentative diagnosis of adrenal tumor was made. At operation no tumor was found, although there were proliferative changes in the adrenal cortex. The patient has been followed for about a year, and there have been no changes in her masculine syndrome. The case was reported by Dr. C. Russell Anderson (*California & West. Med.*).

DR. WILEY M. SAMS, Miami, Fla.: The most interesting thing to me about acanthosis nigricans is to speculate on the mechanism which brings about this change in the skin.

Approximately a year ago I was asked to see a patient who was suspected of having a cancer. It was subsequently found that she had cancer of the breast with metastasis. She had a yellowish discoloration, which was determined to be a carotenosis. It has occurred to me that the acanthosis may be an expression of some nutritional disturbance which brings about the proliferation. My patient was receiving nothing unusual in her diet; I checked it over carefully. She was not eating an unusual amount of provitamin A (carotene). She was taking some vitamin preparations, but they contained no provitamin A. We concluded that her carotenoid pigmentation was due to a failure to metabolize provitamin A, allowing the carotenoid substances to accumulate. The yellowish discoloration was most pronounced not only on the palms and soles but in the areas of acanthosis which had developed beneath the breasts and in the axillas. It occurred

to me at the time, and while following the discussion of this paper, that a nutritional disturbance might possibly underlie the production of the acanthosis nigricans.

DR. FRED D. WEIDMAN, Philadelphia: Dr. Leslie Nicholas has been studying an instance of the malignant form of acanthosis nigricans, the report to be published in the ARCHIVES. The patient came to necropsy showing a most advanced retroperitoneal lymphosarcoma. Surprisingly, there appeared in the histologic sections some small metastases in the subcutaneous tissue. This may be a unique example of actual tumor tissue demonstrated within, or at least below, skin which is involved by acanthosis nigricans.

Of course, metastasis of a malignant growth in the skin is comparatively rare under any circumstances. When it comes to appearing particularly in this pigmented part of the skin, there seems to be some added significance. Certain it is that the amount of tumor tissue in a case of this kind cannot be great; otherwise it could be recognized clinically. The neoplastic infiltration would have been discovered long ago. In Nicholas' case it was not demonstrated. The significance I refer to is this: From the appearance of the metastatic cells, I felt that they were regressive—almost degenerate. Somehow I sensed that possibly some of them could establish only a temporary foothold in the skin—that they would then regress and disappear.

I should like to request that in the future the specimens for biopsy be taken sufficiently deeply to include the subcutaneous fat. There is a tendency to take rather superficial specimens. It may be, if this precaution is taken, that more examples of this metastatic malignant growth under the pigmentary lesions of acanthosis nigricans will be discovered.

DR. DUDLEY C. SMITH, University, Va.: Dr. O'Leary's suggestion that acanthosis nigricans might be an indication for exploratory laparotomy is somewhat unique but, I believe, justified. This condition, then, can be classified as a signal to go ahead and to attempt even major measures for the detection of malignant growth in its earlier stages, when it might be cured.

The fact that Dr. Weidman reported a case of this condition associated with lymphosarcoma throws considerable doubt on one of the hypotheses suggested, that acanthosis nigricans might be related genetically to the background of certain types of carcinoma, particularly those of the visceral glandular type.

Of course, a malignant condition does not have to be present, as Dr. Sams mentioned. There have been examples described from severe, rather general blows over the abdomen, as well as others not related to cancer.

Symposium on Superficial Fungous Infections

IONTOPHORESIS OF COPPER SULFATE IN CASES OF PROVED MYCOTIC INFECTION

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Any one who has used iontophoresis in the treatment of cutaneous diseases will agree with Shaffer [1] that the method is "complicated, technical, tedious and time consuming." If this is so, in order to justify its use its advantage over simpler methods of treatment must be demonstrated.

It will be agreed, we think, that the present status of the treatment of the resistant types of fungous infection is not satisfactory and that the number and variety of therapeutic methods in use prove that no one of them is consistently effective.

Jersild and Plesner [2] have reported the treatment of 137 patients with dermatophytosis by the use of iontophoresis of copper sulfate, with complete cure in 87 per cent. Haggard, Strauss and Greenberg,[3] in 1939, reported using this method in 37 cases, with cure in 70 per cent. In our opinion, these results are better than those ordinarily obtained with any other method. Neither of these series, however, was completely controlled as to the presence of fungi at the beginning of treatment or their absence at the time of the patient's discharge.

This and the following papers were read in a Symposium on Superficial Fungous Infections at the Sixty-Fourth Annual Meeting of the American Dermatological Association, Inc., New Orleans, April 10, 1941.

1. Shaffer, L. W.: Ionic Medication in Dermatology: Experimental Confirmation and Clinical Applications, Arch. Dermat. & Syph. **23**:287-308 (Feb.) 1931.

2. Jersild, O., and Plesner, M.: Treatment of Epidermophytosis on the Extremities with Copper Iontophoresis, Acta dermat.-venereol. **21**:268-279 (March) 1940.

3. Haggard, H. W.; Strauss, M. J., and Greenberg, L. A.: Fungous Infections of the Hands and Feet Treated by Iontophoresis of Copper, J. A. M. A. **112**:1229-1232 (April 1) 1939.

In 1937 Lowenfish [4] experimented with the iontophoresis of a number of metals in cases of fungous infection of the skin and concluded that the procedure was of no value.

In the present experiment we repeated the method used by Haggard, Strauss and Greenberg [3] and in addition controlled it by laboratory proof of the presence of pathogenic fungi. We considered as evidence of fungous infection only positive cultures of material taken from affected areas and selected 4 patients who at their first visit to our office had positive cultures of an identifiable pathogenic fungus. We used 0.2 per cent copper sulfate solution, with 8 milliamperes of current, for twenty minutes, as recommended in the report.

It should be pointed out that we are not questioning the results of these reports. We are considering only one factor in this experiment and attempting to answer the questions: "Does the iontophoresis of copper sulfate kill or delay the growth of dermatophytes? Is improvement or cure of dermatophytosis under such treatment due to the iontophoresis of copper sulfate?"

There may be a criticism that too few cases were used in this experiment to give conclusive answers. We feel that it is not the number of cases but the number of treatments which is important. In the reports mentioned [5] four to six treatments were specified as the requisite number. In our cases we gave at least that number and in 1 case twenty-five treatments, four times as many. Three different pathogens were found, and one of them, Epidermophyton inguinale, is known to be easily destroyed.

REPORT OF CASES

CASE 1.—A man aged 31, a bookkeeper, had suffered from a fungous infection for one and one-half years. The hands and feet were involved. The soles showed deep vesiculation, and there was involvement of the hands which may have been a dermatophytid. Cultures of material from the soles showed Trichophyton gypseum. The intradermal injection of Trichophytin, 0.1 cc. of a 1:30 dilution, elicited a positive reaction. The following treatment was given: 0.2 per cent copper sulfate by iontophoresis, 8 milliamperes, for fifteen to forty minutes twice weekly from June 29, 1940 to November, totaling twenty-five treatments. Cultures and microscopic examinations were made at frequent intervals during the entire course of treatment. It was possible to grow T. gypseum from scales taken at each examination and at the patient's last visit.

CASE 2.—A woman aged 60, a social worker, presented an acute superficial infection of the hand due to T. gypseum and was thought by us to be an especially favorable patient for treatment with copper iontophoresis. She was treated by this method from Aug. 25, 1940 to September 13, receiving six treatments. Scales taken after each treatment gave positive cultures. After the sixth treat-

4. Lowenfish, F. P.: Treatment of Chronic Dermatitis by a Cataphoretic Method, Arch. Dermat. & Syph. **37**:797-804 (May) 1938.

5. Jersild and Plesner.[2] Haggard, Strauss and Greenberg.[3]

ment the process was extending so rapidly that something else had to be used. Compound ointment of benzoic acid was applied on September 19, and since September 29 there has been no obvious activity and all scales and cultures have been negative for T. gypseum.

CASE 3.—A man aged 73, a teacher, presented a clinically active mycotic infection of the feet which had been present for thirty years. Cultures showed E. inguinale. He was treated with copper iontophoresis from Nov. 4, 1940 to December 4, and cultures for the organism were positive after each treatment. In this case a scale so impregnated with copper as to appear solidly green gave six positive cultures from six plants. On Jan. 13, 1941, after the application of compound ointment of benzoic acid, the condition was clinically improved but still active mycologically.

CASE 4.—A man aged 32, a garage mechanic, had suffered for two years with involvement of the feet and hands. Cultures of material from the hands and feet were positive for Trichophytin purpureum. He was treated from June 26, 1940 to July 29 with copper iontophoresis, and positive cultures were obtained during and at the conclusion of this treatment.

COMMENT

It is evident that under the conditions of this experiment the method was neither fungicidal nor fungistatic. There are two reasons at least why this method is ineffective: First, the assumption that copper sulfate is a fungicide for dermatophytes has never been proved. Copper and sulfur compounds are effective protectants against fungi causing diseases in plants, and because this is so it has been assumed that they are likewise effective against dermatophytes. This assumption is, we believe, without experimental proof. McCallan [6] has shown that copper and sulfur compounds are effective against plant pathogens because excretions from the spores of the pathogens put into solution the toxic elements from these compounds and these solutions produce the fungicidal and fungistatic effect. This effect, however, takes place under conditions which do not apply in any way when one is dealing with the action of these substances on dermatophytes.

Emmons [7] stated, in speaking of the fungicidal action of some common disinfectants on dermatophytes:

> It is surprising to find copper sulphate so ineffective. It is used in the preparation of Bordeaux mixture, which controls fungous diseases of plants and is effective in a dilution of 1: 1,000,000 in preventing the growth of certain algae in reservoirs. . . . Under the conditions of this experiment, spores of T. gypseum and M. albicans exposed for thirty minutes to a dilution of 1 part of copper

6. McCallan, S. E. A.: Studies on Fungicides: III. The Solvent Action of Spore Excretions and Other Agencies on Protective Copper Fungicides, Memoir 128, Cornell University Agricultural Experiment Station, May 1930.

7. Emmons, C. W.: Fungicidal Action of Some Common Disinfectants on Two Dermatophytes, Arch. Dermat. & Syph. **28**:15-21 (July) 1933.

sulphate to 4 parts of water readily grew when transferred to broth. This was tried repeatedly and was further checked by the use of spores of other fungi which also survived this treatment.

He also stated that whereas iodine as a fungicide has a phenol coefficient of 3,000, the value of copper sulfate expressed in the same terms is zero.

A second explanation of the inefficacy of copper iontophoresis as a fungicidal method involves a discussion of the fate of copper sulfate introduced into the skin by electrophoresis. It is probable that some of the copper is deposited on the cutaneous surface, where it combines with the proteins of the skin to form copper albuminates. An uncertain number of the ions may be carried away by the blood and lymph to be deposited elsewhere in the body; the depth of penetration and the time required for penetration are unknown, but the depth is probably slight and the time required for penetration long. Turrell [8] stated that the effects of electrophoresis are probably due to the heat generated by the electric currents rather than to the medicaments used. It is reasonable to conclude that even if copper sulfate were effective as a fungicide for dermatophytes, it would be doubtful if sufficient amounts reached the pathogens or remained in contact with them long enough or in a suitable form to be effective. However, the discussion of so complicated a process as iontophoresis would bring up many questions which are outside the scope of this experiment.

CONCLUSION

Under the conditions of this experiment, copper sulfate introduced into the skin by iontophoresis is neither fungicidal nor fungistatic for T. gypseum, T. purpureum or E. inguinale. When there is clinical improvement from this treatment it must be due to some factor or factors other than the copper sulfate.

8. Turrell, W. J.: The Action of the Constant Current with Special Reference to Its Action on the Subcutaneous Tissues, Arch. Radiol. & Electroth. **27**:130-135 (Sept.) 1922.

UNDENATURED TRICHOPHYTIN

PREPARATION AND CLINICAL APPLICATION

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Fungous infections have a tendency to induce hypersensitive states. This outstanding characteristic is found in the superficial and deep mycoses. These allergic conditions are frequently manifested by eruptions called ids. The trichophytids and moniliids (or levurids) are well known. Sporotrichids in sporotrichosis have been described by de Beurmann.[1] The erythema nodosum which is often associated with primary coccidioidomycosis may be considered the id in this disease. Thus, fungous infections present problems of immunology that are peculiar to themselves, although they are perhaps related to diseases such as tuberculosis and syphilis, in which ids also occur.

The present concepts of the hypersensitive states, the allergy of infection, have been developed to a greater extent from microbian diseases than from mycotic infections. Because of the relative infrequency of deep mycotic infections, it is difficult to obtain sufficient material for analysis. As a result, interpretations of the immunologic reactions between the host and the fungus too frequently are based on reasoning by analogy. Goddard [2] and Stewart and Meyer [3] investigated the physiologic and metabolic states of the dermatophytes and of two organisms representative of those causing deep mycoses, Coccidioides immitis and Blastomyces dermatitidis. The results showed that the metabolism

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Read in a symposium on Superficial Fungous Infections at the Sixty-Fourth Annual Meeting of the American Dermatological Association, Inc., New Orleans, April 10, 1941.

1. de Beurmann: Sporotrichosis, Brit. M. J. **2**:289, 1912.

2. Goddard, D. R.: Phases in the Metabolism of Trichophyton Interdigitale (Priestly), J. Infect. Dis. **54**:149-163, 1934.

3. Stewart, R. A., and Meyer, K. F.: Studies on the Metabolism of Coccidioides Immitis (Stiles), J. Infect. Dis. **63**:196-205, 1938.

(physiology) of the fungi sharply distinguished them from bacteria, protozoa and certain actinomycetes and demonstrated the fallacy of applying bacteriologic principles of metabolism to fungi. It is therefore possible that the present concepts of the hypersensitive states induced by fungous infections are in error so far as they rely for interpretation on analogies to bacterial infections.

The incidence of coccidioidal infection in California prompted a study of the immunologic reactions in this disease. During the early studies on the coccidioidin cutaneous test [4] several types of antigens were investigated. The undenatured antigens prepared by the Krueger method [5] were more uniform in strength and gave fewer nonspecific reactions than other antigens, and the process of making and standardizing them was subject to satisfactory control. Well controlled and uniform laboratory methods are essential before parallel investigations of the immunologic reactions of the deep and of the superficial mycoses can be undertaken. It was necessary, therefore, to determine the value of undenatured antigens in the studies of a superficial mycosis before proceeding with the combined investigations. Because dermatophytosis is the most common superficial mycosis, the preliminary studies were made on this disease.

No attempt was made to approach all the phases associated with the allergic state induced by the dermatophytes, but attention was directed to the demonstration of three facts: first, that undenatured antigens induce antibody formation in experimental animals; second, that the antigens are suitable for the performance of serologic reactions with the serums of animals and of human beings, and, third, that satisfactory clinical investigations may be carried out to determine the specificity of cutaneous tests and the value of therapeutic injections for desensitization.

MATERIAL AND METHODS

Organisms.—The organisms used were Trichophyton interdigitale (Priestly), Epidermophyton cruris (Castellani and Chalmers) and Trichophyton rosaceum (Sabouraud). Legge, Bonar and Templeton [6] found that in their studies of dermatophytosis at the University of California these three organisms occurred most frequently and in the order named.

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4. Stewart, R. A., and Kimura, F.: Studies in the Skin Test for Coccidioidal Infection, J. Infect. Dis. **66**:212-217, 1940.

5. Krueger, A. P.: A Method for the Preparation of Bacterial Antigens, J. Infect. Dis. **53**:237-238, 1933.

6. Legge, R. T.; Bonar, L., and Templeton, H. J.: Epidermomycosis at the University of California: Study III, Arch. Dermat. & Syph. **27**:12-24 (Jan.) 1933.

Culture Medium.—Cultures were grown in Blake bottles at room temperature for five days. A modification of Leonian's medium was used. The formula was:

Monobasic potassium phosphate	1.25 Gm.
Magnesium sulfate	0.63 Gm.
Maltose (or dextrose)	6.25 Gm.
Malt extract	6.25 Gm.
Distilled water	1,000.00 cc.

Unlike the growth which develops on a rich medium, such as Sabouraud's, that in this medium is almost entirely of loose mycelial nature. Harvesting and washing in the centrifuge is therefore possible. The total crop after four to five days' incubation is about two thirds of that on Sabouraud's medium; however, the desired type of growth more than compensates for this loss.

Preparation.—The harvested fungus crop is washed three or four times in Locke's solution containing 1:50,000 to 1:100,000 parts merthiolate. This process leaves the minimum amount of culture medium and metabolites in the final product. Washed cultures from forty to fifty Blake bottles together with 150 to 200 cc. of Locke's solution are triturated in a ball mill for eighteen hours. The macerated substance is filtered through ultrafilters made with 1 to 1.5 per cent acetic collodion membranes (Krueger and Ritter [7]).

Standardization.—A. Nitrogen Content: The standardization of trichophytin is difficult because no method has been found for comparing the antigenic strength or content of the various preparations. Although most investigators agree that the active principle is apparently associated with a polysaccharide, they are not able to standardize the antigens on the basis of this substance. Bloch, Labouchère and Schaaf [8] succeeded in isolating a starchlike polysaccharide which contained nitrogen but had no protein fraction. This substance when inoculated elicited a positive cutaneous reaction like that obtained with trichophytin. In this respect it is similar to the coccidioidin of Hirsch and Benson.[9] It was active in high dilution and elicited positive Schultz-Dale reactions for sensitivity. According to Bloch, Labouchère and Schaaf it seems advisable to rely for the present on the nitrogen content of

7. Krueger, A. P., and Ritter, R. C.: The Preparation of a Graded Series of Ultrafilters and Measurement of Their Pore Size, J. Gen. Physiol. **13**:409-419, 1930.

8. Bloch, B.; Labouchère, A., and Schaaf, F.: Versuch einer chemischen Characterisierung und Reindarstellcng des Trichophytins, Arch. f. Dermat. u. Syph. **148**:413-424, 1925.

9. Hirsch, E. F., and Benson, H.: Specific Skin and Test Reactions with Culture Filtrates of Coccidioides Immitis, J. Infect. Dis. **40**:629-633, 1927.

trichophytin for standardization. Goodman and Marks [10] and Traub and Tolmach [11] also reported on a trichophytin that was standardized by its nitrogen content. Both the total nitrogen and the precipitable protein nitrogen were determined by the micro-Kjeldahl method. The precipitable nitrogen was obtained by adding to an aliquot of the trichophytin an excess of 5 per cent sodium tungstate, containing 2 per cent sodium sulfate, and precipitating with 2 per cent copper sulfate in fifth-normal sulfuric acid. The results of this standardization are given in table 1.

B. Denaturation: The amount of denaturation was determined by the method described by Krueger and Nichols.[12] The isoelectric point of bacterial protein was p_H 4.45. The isoelectric point of trichophytin protein was also p_H 4.45. The citric acid–sodium hydroxide buffer system was used to precipitate the denatured protein, and a Kjeldahl determination on this precipitate revealed the nitrogen content of the denatured protein. The amount of protein denatured was 8.9 per cent.

TABLE 1.—*Nitrogen Determinations by Micro-Kjeldahl Method*

Trichophytin	Nitrogen, Mg. per 100 Cc.		
	Total	Precipitable	Total for Clinical Use
T. interdigitale	62.72	4.61	60.00
E. cruris	77.98	3.20	60.00
T. rosaceum	85.82	1.68	60.00

Sterility Test.—Standardized trichophytin and various dilutions of it were bottled, and sterility tests were made on each sample before it was used. For this purpose aliquots of 0.5 cc. were inoculated into nutrient broth and brain medium and incubated for forty-eight to seventy-two hours.

EXPERIMENTAL PROCEDURES

Immunization of Animals.—Rabbits were inoculated with the antigens twice a week for six weeks. The schedule is given in table 2. The serums of these animals were tested for complement-fixing antibodies and precipitins. No attempt was made to test them for agglutinins, for a uniform turbidity of spore suspension was difficult to obtain. Moreover, the agglutinin titer would be expected to be relatively low, for

10. Goodman, H., and Marks, I.: Reactions to Trichophytin Compared with Reactions to Other Bacterial Products, Arch. Dermat. & Syph. **31**:819-827 (June) 1935.

11. Traub, E. F., and Tolmach, J. A.: Dermatophytosis: Its Treatment with Trichophytins, Arch. Dermat. & Syph. **32**:413-421 (Sept.) 1935.

12. Krueger, A. P., and Nichols, V. C.: The Denaturation of Staphylococcal Proteins, J. Bact. **30**:401-409, 1935.

according to the work of Merrill [13] the mass of the antigen is important in the production of certain antibodies.

Complement fixation was tested by the Kolmer method. A titer of 1/80 was obtained in a 1 to 5 dilution of trichophytin. This dilution, which contained 0.15 mg. of nitrogen per cubic centimeter, was chosen arbitrarily and compared with other dilutions for activity. Since there is no standard serum or method to test this activity, the results of this experiment served as a means of standardizing later determinations. The trichophytins were ideal as "Kolmer" antigen, for they were not anticomplementary or hemolytic.

The animals responded by the production of precipitins as a result of the immunization process. In testing for precipitins a slight modifica-

TABLE 2.—*Dosage Schedule for the "Immunization" of Six Rabbits (Two for Each Antigen) with Trichophytins of T. Interdigitale, E. Cruris and T. Rosaceum*

Week	Dose	Route
First	0.5 cc. 1.0 cc.	Subcutaneous
Second	1.5 cc. 2.0 cc.	Intraperitoneal
Third	2.0 cc. 2.0 cc.	Intravenous
Fourth	2.0 cc. 2.0 cc.	Intravenous
Fifth	2.0 cc. 2.0 cc.	Intravenous
Sixth	2.0 cc. 2.0 cc.	Intravenous
Seventh	(Bled)	

tion of Hanks's precipitin method [14] was used. The trichophytin was added to a base composed of 5 Gm. of gelatin dissolved in a mixture of 20 per cent glycerin and 80 per cent Locke's solution. The base was adjusted to a p_H of 7.4. By repeated titrations (testing with various dilutions of trichophytin) it was found that a 1 to 5 dilution is optimal for this test as for the Kolmer test. A ratio of 1 part antigen to 1 part gelatin base gave the clearest and most consistent results. Small clean agglutination tubes containing 0.4 cc. portions of this mixture were placed in the icebox for eighteen hours. The mixture was maintained in a jelled state, and 0.6 cc. of antiserum dilutions were layered onto the antigen base and incubated for three hours. The tubes then were carefully placed in the ice box for forty-eight hours. Tubes containing serum and Locke's

13. Merrill, M. H.: The Mass Factor in Immunologic Studies upon Viruses, J. Immunol. **30**:169-184, 1936.

14. Hanks, J. H.: A Ring Precipitin Test for Estimating the Concentration of Antibody in Small Amounts of Immune Sera, J. Immunol. **28**:95-104, 1935.

solution were included as a control for each test. The white ring at the interface of the antiserum and the antigen-base mixtures denoted precipitation. The results are tabulated in tables 3 and 4, together with cross sections to determine specificity.

Specificity of Immune Bodies.—An attempt was made to demonstrate any cross immunization by means of these tests. The complement fixation test with 1 to 5 antigen was not sensitive enough to bring out conclusively the presence or absence of cross reactions in three serums and antigens. On the other hand, the precipitin test showed interesting

TABLE 3.—*Serologic Cross Reactions of Serums of Rabbits Immunized with Trichophytins: I. Precipitin Test*

	Antiserums																	
	T. Interdigitale						E. Cruris						T. Rosaceum					
Antigen (1:5)	1: 8	1: 16	1: 32	1: 64	1: 128	1: 256	1: 8	1: 16	1: 32	1: 64	1: 128	1: 256	1: 8	1: 16	1: 32	1: 64	1: 128	1: 256
T. interdigitale.....	+	+	+	+	−	−	−	−	−	−	−	−	+	+	+	±	−	−
E. cruris.....	+	+	+	±	−	−	+	+	+	+	−	−	+	+	+	±	±	−
T. rosaceum.....	+	+	+	±	−	−	−	−	−	−	−	−	+	+	+	+	+	−

TABLE 4.—*Serologic Cross Reactions of Serums of Rabbits Immunized with Trichophytins: II. Complement Fixation Test*

	Antiserums																	
	T. Interdigitale						E. Cruris						T. Rosaceum					
Antigen (1:5)	1: 5	1: 10	1: 20	1: 100	1: 200	Control	1: 5	1: 10	1: 20	1: 100	1: 200	Control	1: 5	1: 10	1: 20	1: 100	1: 200	Control
T. interdigitale.....	+	+	+	+	−	−	∓	−	−	−	−	−	∓	∓	−	−	−	−
E. cruris.....	∓	−	−	−	−	−	+	+	+	+	−	−	∓	−	−	−	−	−
T. rosaceum.....	+	∓	−	−	−	−	∓	−	−	−	−	−	+	+	+	+	∓	−

results. No precipitins for trichophyton organisms were found in the E. cruris antiserum, but there were precipitins for epidermophyton organisms in trichophyton antiserums (table 3). There is no satisfactory explanation for the reactions between trichophyton antiserums and epidermophyton antigen at this time.

CLINICAL INVESTIGATIONS

Clinical studies were carried out in the dermatologic clinic at the University of California Hospital. Subjects were selected from among volunteer medical and dental students and regular patients. Diagnoses were based on history, clinical appearance and laboratory procedures. Laboratory procedures were, however, disappointing, and the percentage of positive results was too low to be included in detail in a preliminary report of this kind. The presence of fungi could not be demonstrated

microscopically in more than 80 per cent of the cases. Cultural confirmation was obtained in 65 per cent of the cases. These results are in agreement with those reported by Legge, Bonar and Templeton.[6] The laboratory results are therefore not reported in detail.

Cutaneous Tests.—In order to simplify the investigations, only the antigen prepared from T. interdigitale was used. The selection was based on the results of the investigations of Legge, Bonar and Templeton,[6] who demonstrated that this organism predominated in the cases studied at the University of California.

A 1 to 5 dilution of T. interdigitale antigen, containing 0.12 mg. of nitrogen per cubic centimeter, was found satisfactory and sufficient for routine cutaneous tests. By preliminary clinical trial it was found that a 1 to 10 dilution of trichophytin was likely to be inadequate for routine tests and that a full strength antigen tended to produce an unnecessarily strong reaction. Each patient received an injection of 0.1 cc. of the 1 to 5 dilution of trichophytin intradermally on the flexor surface of the forearm (26 gage needles and tuberculin syringes were used exclusively for these tests). Readings were taken in twenty-four to seventy-two hours after inoculation, and the size and the degree of the reaction were recorded. Positive responses were characterized by an erythematous area occasionally accompanied by vesicular or eczematous reactions. Control injections were not made, as responses to these had proved to be uniformly negative in experiments on animals and in observations on human beings, probably because the antigen is relatively free from constituents of the culture medium.

The results of tests of sensitivity to trichophytin in 208 patients are recorded in table 5. Approximately 17.78 per cent of the subjects for whom a clinical diagnosis of dermatophytosis (with or without the id), was made showed no sensitivity. Positive reactions were elicited in 171 cases. Table 6 shows the distribution of reactions in patients in age groups below and above 35 years. In 85.7 per cent of those above 35 and in 81 per cent of those below 35 there was sensitivity to T. interdigitale antigen. Table 7 shows the distribution of clinical manifestations of the "ringworm" infection on the various parts of the body. The relation of the reactions to the cutaneous tests to the location of the lesions is also tabulated. These results are essentially in agreement with those summarized by Lewis and Hopper.[15]

Instances of wheal formation immediately after injection of trichophytin were rare, although Sulzberger [16] and Marcussen [17] emphasized

15. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, Chicago, The Year Book Publishers, Inc., 1940.

16. Sulzberger, M. B.: Experiments in Passive Transference of Urticarial Hypersensitiveness to Fungus Extracts, J. Immunol. **23**:73-79, 1932.

17. Marcussen, P. V.: Relationship of Urticarial to Inflammatory Reaction to Trichophytin, Arch. Dermat. & Syph. **36**:494-514 (Sept.) 1937.

the occurrence of these reactions. Marcussen, however, noted the possibility that these reactions may have resulted from some substance in the trichophytin, such as peptone. No examples of general reaction similar to hay fever or asthma were noted. However, in some cases the lesions flared up in response to trichophytin. Three instances of delayed

TABLE 5.—*Results of Cutaneous Tests with Trichophytin (T. Interdigitale) of Two Hundred and Eight Patients of All Ages with Clinical Diagnosis of Dermatophytosis*

Reaction	Strength of Trichophytin			Total	
	Full	1:5	1:10	Number	Per Cent
Positive					
Definite	9	147	6	162	77.8
Mild	3	3	..	6	2.8
Doubtful	1	2	..	3	1.4
Total	..	..	..	171	82.10
Negative	10	27	..	37	17.78

TABLE 6.—*Reactions to Trichophytin (T. Interdigitale) in Two Hundred and Eight Patients in Age Groups Below and Above Thirty-Five Years*

Reaction	Above 35 Years	Below 35 Years	Age Unknown	Total
Positive				
Definite	62	99	1	162
Mild	2	3	1	6
Doubtful	2	1	..	3
Total	66	103	2	171
Negative	11	24	2	37

TABLE 7.—*Relation of Reactions to Cutaneous Tests with Trichophytin to Location of the Infection*

Location of Infection	Number of Cases	Positive Reaction		Negative Reaction	
		Number	Per Cent	Number	Per Cent
Feet and hands	93	75	80.5	18	19.5
Feet	70	62	88.5	8	11.4
Hands	23	13	55.5	10	43.4
Feet and crural region	19	18	94.8	1	5.3
Not stated	3	3	10.0	..	....

response were noted. The time interval between injection and appearance of delayed reaction was from five to seven days.

Therapy.—The patients were divided into three groups. The first group received local treatment with the usual soaks, ointments and lotions. The second group received local therapy and, in addition, injections of antigen. The third group received only injections of antigen.

The method of treatment by desensitization that was followed in this study differs from that of previous investigations. By the usual method

that concentration which produces the cutaneous reaction is chosen for the initial dose. Some authors choose an arbitrary dilution of 1 to 50, 1 to 100 or, rarely, 1 to 1,000. Fairly large amounts, 0.2 to 0.4 cc., are administered intradermally until no local reaction is produced with that concentration. This presumably constitutes an indication to use the next higher dilution. The procedure is continued until the patient is able to tolerate an injection of full strength antigen and therefore is considered sufficiently desensitized.

In our opinion this dosage is too large. We felt that if more dilute trichophytin were used, there might be a gradual desensitization process which would induce a more favorable reaction in the lesions. Therefore dilutions of 1 to 100,000, 1 to 10,000, 1 to 1,000 and 1 to 100 and full

TABLE 8.—*Results of Treatment*

Reaction to Cutaneous Test	Patients, No.	Treatment		Results									
				Cured		Improved		Slight Improvement		No Improvement		Recurrence	
		Type	No.	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Negative	25	Local only	21	8	38.1	9	44.9	4	19.0	..	....	7	41.2
		Local plus injections	4	2	50.0	2	50.0	..	....	..	....	3	75.0
		Injections only	..	..	....	..	....	..	....	..	....	..	....
Positive	138	Local only	38	15	39.4	20	52.6	3	7.9	..	....	7	20.0
		Local plus injections	73	28	38.4	38	52.1	7	9.6	..	....	13	19.7
		Injections only	27	13	48.1	13	48.1	..	...	1	3.7	11	42.3

strength antigen were used. All dilutions were made in Locke's solution. Patients were given 0.1 cc. of 1 to 100,000 trichophytin once a week as long as the response was favorable. If the symptoms were not lessened, the next higher concentration was administered. Thus, the evaluation of dosage depended on the reaction of the lesion and not on sensitivity of the skin. In a few instances injections were attempted every three days, but the interval was extended to seven days when it became apparent that the infection tended to flare up. During the first few trials of treatment, the subcutaneous route of injection was employed, but the therapeutic effect was low; when the intradermal route was instituted a decided improvement was noted. For this reason the intradermal method of injection has been adopted.

The results of treatment are tabulated in table 8. The patients were divided into two groups, dependent on the results of the cutaneous test. Recurrences are also recorded. The period of observation was eight months. The average number of injections given was twenty. The

largest number of injections was twenty-five and the smallest four. It would appear from the table that the subjects who received injections of the antigen enjoyed greater improvement than those who received local therapy only. This effect is offset by the larger percentage of recurrences in the group treated only with injections of antigen. It is not possible to compare the groups scientifically with respect to the time element. The patients with acute dermatophytosis with or without concomitant ids almost invariably required local therapy, especially those who also had an associated pyogenic infection. Most of those who received only injections of antigen or injections of antigen supplemented by local treatment had chronic dermatophytosis.

TABLE 9.—*Quantitative Antibody Study in Selected Patients with Superficial Dermatophytosis*

	Complement-Fixing Antibodies Serum Dilution						Precipitin Antibodies Serum Dilution				
Patient	1:5	1:10	1:20	1:100	1:200	Control	1:16	1:32	1:64	1:128	Control
1	—	—	—	—	—	—	+	+	+	+	—
2	—	—	—	—	—	—	+	+	+	+	—
3	+	+	—	—	—	—	+	+	+	+	—
4	++++	++++	++++	+	+	—	+	+	—	—	—
5	—	—	—	—	—	—	+	+	+	+	—
6	—	—	—	—	—	—	+	+	—	—	—
7	—	—	—	—	—	—	—	—	—	—	—
8	—	—	—	—	—	—	+	+	+	—	—
9	—	—	—	—	—	—	—	—	—	—	—
10	++	++	++	+	+	—	+	+	—	—	—
11	—	—	—	—	—	—	—	—	—	—	—
12	—	—	—	—	—	—	++	+	+	—	—
13	—	—	—	—	—	—	+	+	—	—	—
14	—	—	—	—	—	—	+	—	—	—	—
15	—	—	—	—	—	—	—	—	—	—	—

It would obviously be a mistake to discuss any conclusions that are not within the limits of the experimental method employed. In the present studies the sole object was to determine whether or not the undenatured antigens could be used clinically. Later experiments will determine the efficacy of the antigens with respect to the length of time required to obtain remissions or cures.

Serologic Determinations.—Lewis and Hopper [15] reported that antibody formation in persons with fungous infections has not been unequivocally demonstrated. By the same technic as that described in experimental procedures, the serums of 15 typical patients who had dermatophytosis were tested for the presence of complement-fixing antibodies and precipitins (table 9). Two of the patients showed a high titer of complement-fixing immune bodies, and 1 patient gave a slightly positive reaction. The results of the precipitin tests show that these antibodies are produced in the majority of the cases. Hanks's method of testing for precipitins appears to give satisfactory results.

COMMENT

Sulzberger [18] has emphasized the fact that the allergenic properties and constituents of the different trichophytin preparations vary. He has also observed variations in two trichophytins made at different times from cultures of the same strain. Usually Bloch's method is employed for the production of the average antigen. The essential principles of his method are: 1. The desired culture is grown in Sabouraud's medium. 2. The resulting growth is triturated in a sterile mortar with solid carbon dioxide, the culture solution serving as the menstruum. 3. This mixture is shaken, incubated and finally filtered through a sterile Chamberland filter; the antigen is then standardized biologically by comparing its strength with that of similar extracts of known potency.

All trichophytins prepared by this or similar methods are composed of three fractions: (1) the culture solution, (2) the various metabolic products of the culture and (3) the extractives from the organism. The situation is complicated further because culture solutions vary even when they are made by the same formula. This variation is due in part to the differences in the many brands of peptone which are available. The differences in peptones are recognized by the bacteriologists who have studied the production of specific toxins, such as diphtheria and botulism toxins. Goddard [2] indicated that variations in the culture solutions affect certain phases of the metabolism of T. interdigitale. From these considerations the need for antigens which are produced by methods that can be controlled and duplicated is evident.

The preparation of undenatured antigens is based on the fact that many of the antigenic components of bacteria are labile to the action of heat and chemicals. This observation is not particularly surprising, as many of the cellular components are proteins and proteins in general are fairly easily denatured.[19] Krueger and Nichols [12] have shown that bacterial proteins are just as easily denatured. Presumably the same is true of fungi. Krueger antigens are of uniform potency, and the method of preparing them has been standardized. The satisfactory coccidioidin prepared by this method [4] suggests the use of similar antigens for a superficial mycosis, dermatophytosis. From the outset it was apparent that the scope of the preliminary studies would have to be strictly limited. The essential thing was to determine the value of undenatured trichophytin for laboratory and clinical use. The results of the investigations are essentially in agreement with those obtained by Lewis and Hopper.[15]

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18. Sulzberger, M. B.: Dermatologic Allergy, Springfield, Ill., Charles C. Thomas, Publisher, 1940.

19. Anson, M. L., and Mirskey, A. F.: On Some General Properties of Proteins, J. Gen. Physiol. **9**:169-174, 1925-1926.

The allergy of dermatomycosis constitutes a broad and complicated subject. Many problems connected with it should be investigated with the undenatured antigens. One problem immediately suggests itself, namely: What is the nature of the antigenic components responsible for the serologic reactions and cutaneous reactions? Undenatured trichophytin apparently contains at least two reactive fractions. If trichophytin is dialyzed for forty-eight hours in collodion membranes against running tap water, the residuum does not give the same percentage of positive cutaneous reactions as the original substance. For example, 10 patients who had previously reacted to trichophytin were retested with both the dialyzed and the original substance. Five patients reacted to both injections; 3 reacted to only the original undenatured trichophytin, and 2 reacted to only the dialyzed antigen. The significance of this result is not apparent at present. It is interesting to note that the substance in coccidioidin [4] responsible for the cutaneous reaction is dialyzable and is apparently a polysaccharide.

It is hoped that future studies on the undenatured antigens may reveal further similarities between the superficial and the deep mycoses.

SUMMARY AND CONCLUSIONS

A method for preparing undenatured trichophytin is presented.

The method is subject to suitable control and eliminates many variable factors that are associated with the preparation of fungus antigens.

The undenatured trichophytin stimulates the production of complement-fixing antibodies and precipitins when injected into rabbits.

The antigen is suitable for use in serologic tests to detect the presence of circulating antibodies in human infections.

The results of cutaneous tests on 208 patients with dermatophytosis are given.

Preliminary studies on the therapeutic effect of undenatured trichophytin are reported.

TRICHOPHYTIN

II. THE APPARENT SEPARATION OF THE SKIN-REACTIVE FACTOR FROM THE THERAPEUTIC PRINCIPLE IN TRICHOPHYTIN

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In a previous communication [1] it was shown that Trichophyton gypseum was capable of producing a more alkaline p_H in Sabouraud's bouillon when grown on a medium with an initial p_H of 4.0 to 8.0. At an initial p_H of 9.0 to 10.0 the organism acidified the medium. There was occasionally acidification in buffered solutions which had an initial p_H of 7.0. At the end of variable periods of growth, approximately seventy-five to eighty days, the hydrogen ion concentration would finally become stabilized at a p_H of 8.3 to 8.6.

We were able to demonstrate in experiments embodied in a recent paper [2] that the component of trichophytin capable of eliciting a positive reaction to a cutaneous test was found in the bouillon itself as well as in the pellicle of a culture in Sabouraud's bouillon.

A number of observers have maintained that this skin-reactive factor in trichophytin was not necessarily identical with the therapeutic or immunizing principle. It was this possibility that led da Fonseca

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Read in a symposium on Superficial Fungous Infections at the Sixty-Fourth Annual Meeting of the American Dermatological Association, Inc., New Orleans, April 10, 1941.

From the Laboratories and Service of Dr. Isadore Rosen, Mount Sinai Hospital, and from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital.

1. (*a*) Peck, S. M., and Rosenfeld, H.: The Effects of Hydrogen Ion Concentration, Fatty Acids and Vitamin C on the Growth of Fungi, J. Invest. Dermat. **1**:237, 1938. (*b*) Peck, S. M.; Rosenfeld, H.; Leifer, W., and Bierman, W.: Role of Sweat as a Fungicide, Arch. Dermat. & Syph. **39**:126 (Jan.) 1939.

2. Peck, S. M., and Glick, A.: Trichophytin: I. Methods of Preparation with Special Reference to the Specific Skin-Reactive Factor, Arch. Dermat. & Syph. **43**:839 (May) 1941.

and his co-workers [3] to prepare two different types of trichophytin extracts. One, which they called "dermotricofitin," was said to contain only the skin test principle, and the other, the "clasovaccine," was thought to have only therapeutic properties and no skin-reactive factor.

It can readily be seen how important such a separation would be from both the theoretic and the practical viewpoint. Large quantities of "clasovaccine" could be administered, rapid desensitization thus being insured without fear of local or general reactions.

Unfortunately, Sulzberger, Lewis and Wise [4] and my collaborators and I have been able to demonstrate the skin test principle in the "clasovaccines." However, such a demonstration of skin test principle does not necessarily obviate a possible separation of these two factors.

It is not unreasonable to conceive the possibility that the chemical substances which are formed in Sabouraud's bouillon after acidification probably have entirely different properties than those giving rise to a more alkaline p_H. These chemical substances, if they are not identical with either the skin test principle or the immunizing factor, might at least have some bearing on their formation and concentration.

A series of experiments was planned to study the relation between the acidifying and alkalinizing substances formed in Sabouraud's bouillon and the skin test and therapeutic factors. Mediums of a wide range of hydrogen ion value were inoculated with T. gypseum. As changes in the hydrogen ion values occurred during growth, fractions were taken from the bouillon. The properties of these fractions were then investigated for the skin test factor and the therapeutic principle.

MATERIAL AND METHOD OF EXPERIMENTATION

Preparation of Mediums.—Sabouraud's bouillon as it was used in our experiments was prepared by adding 20 Gm. of dextrose and 10 Gm. of neopeptone (Difco) to 1 liter of distilled water. It was then put into an Arnold sterilizer for ten minutes and finally filtered through Whatman's no. 4 filter paper while the solution was still hot.

In some of the experiments a 10 × concentration of Sabouraud's bouillon was used. This was prepared by dissolving the same amount of dextrose and neopeptone in 100 cc. of distilled water. This solution was then put into the Arnold sterilizer for ten minutes, filtered through

3. da Fonseca, O., Jr., and de Arêa Leão, A. E.: Vaccinotherapeia das epidermophyceas e das tenhas tonsurantes, Rev. med.-cir. do Brasil **39**:269, 1931. da Fonseca, O., Jr.: Allergedes mycosicas, ibid. **42**:287, 1934. da Fonseca, Jr.; de Arêa Leão, A. E.; Gonsalves Botafogo, N., and Rabello, Jr.: Sobre a natureza da substancia activa nas claso-vaccinas mycosicas, ibid. **44**:31, 1936.

4. Sulzberger, M. B.; Lewis, G. M., and Wise, F.: Trichophytin and Allergy to Trichophytin, Arch. Dermat. & Syph. **34**:207 (Aug.) 1936.

the same type filter paper while hot and then autoclaved at 10 pounds' (4.5 Kg.) pressure for ten minutes just before use. This last step was usually added to insure sterility, for the concentrated medium was usually stored away as a stock solution.

Strains Used.—Several strains of T. gypseum were used. In one of our series of experiments Trichophyton purpureum instead of T. gypseum was used.

Methods of Adjustment of p_H Concentration.—All of our p_H readings were made with the Beckman p_H meter using glass and calomel (mild mercurous chloride) electrodes.

Method 1: Twenty per cent sodium hydroxide solution (five times normal) and concentrated hydrochloric acid (approximately twelve times normal) were used. To adjust the bouillon to an alkaline p_H, we added enough of the sodium hydroxide solution to 1 liter of bouillon to attain the required hydrogen ion concentration. For example, it required

TABLE 1.—*McIlvaine's Buffers*

p_H Required	Disodium Hydrogen Phosphate Solution, Cc.	Citric Acid Solution, Cc.
4.0	7.71	12.29
8.0	19.45	0.55
8.75	Solution as is	None
10.0	40 cc. of phosphate solution plus 20 drops normal sodium hydroxide solution	None

about 2 cc. of the sodium hydroxide solution in 1 liter of ordinary bouillon, with an initial p_H of 6.5, to attain a p_H value of about 8.5. To adjust the bouillon to an acid reaction, concentrated hydrochloric acid was added in the required amount to 1 liter of Sabouraud's bouillon. It usually required about 1 cc. of the acid to give a p_H of approximately 4.0.

Method 2: McIlvaine's buffers were added to Sabouraud's bouillon in the proper amounts to obtain the range of hydrogen ion concentrations necessary for our experiments.[5] McIlvaine's buffers consist of 0.2 molar solution of disodium hydrogen phosphate and 0.1 molar solution of citric acid. Varied proportions of these two chemicals give a range of hydrogen ion concentration from 2.0 to 8.0. It was usual for us to add 2 cc. of the required buffer mixture to 8 cc. of the medium. This gave a final buffer concentration of 1:5. To compensate for the dilution of the nutrient material because of the addition of buffer, for every 10 cc. of buffer used, 1 cc. of 10 × Sabouraud bouillon was added. Table 1 gives the required amounts of components of McIlvaine's buffers

5. Clark, W. M.: The Determination of Hydrogen Ions, ed. 2, Baltimore, Williams & Wilkins Company, 1922, p. 116.

which were used to give the particular p_H values in which we were mainly interested.

We found that in trying to adjust the medium to the more alkaline values, the mixture of buffer, bouillon and 10 × concentrated Sabouraud bouillon caused the p_H to drop. It was thus necessary to readjust the p_H value to the desired level by adding more alkali (20 per cent sodium hydroxide). The p_H value of the mixture usually dropped again after filtration through a Seitz filter. To compensate for this we found it practical to adjust the p_H of the original material as much as 0.8 to 1.8 higher than that of the final desired filtered mixture. Such a step was unnecessary in the more acid p_H range, as there was practically no change after filtration.

It is important to note that there is a decided variation in the p_H values attained by adding equivalent amounts of Difco neopeptone to the same amount of distilled water and sugar. This might be due to an actual difference in the buffering action of the neopeptone or, what is even more likely, to the difference in the initial p_H of the distilled water.

The mixture of the bouillon buffer and 10 × concentrated Sabouraud bouillon when adjusted to a higher alkaline p_H usually gave rise to a precipitate. This solution must be filtered through filter paper so that it will not clog the Seitz filter. This precipitate can also be used as a culture medium and apparently does not change the culture value of the filtrate.

Method 3: Barbital was used as a buffer instead of the phosphate in one series of experiments.[6] The buffering agents consist of soluble barbital dissolved in carbon dioxide–free water and tenth-normal hydrochloric acid (tenth molar solution). The proper mixtures of these solutions gave a p_H range from about 6.4 to 9.8. The preparation of the mediums, with the exception of the use of barbital instead of phosphate, was carried out in the same manner as for method 2.

Tabulation of Data.—During the performance of the experiments two series of culture flasks were used. In one the p_H was markedly acid (approximately 4.0), and in the other the p_H was on the alkaline side (usually 8.0 to 10.0). In the description of the experiments instead of referring to methods 1 and 2 for the technic employed in attaining the required hydrogen ion concentration it was usual to speak of bouillon with and without buffer. In each experiment ordinary Sabouraud bouillon at a p_H of approximately 6.5 was used as a control. A number of flasks of bouillon on both the acid and the alkaline side were always left uninoculated to serve as controls for possible spontaneous fluctuations in the p_H values.

6. Michaelis, L.: Veronal Buffer (Veronal Sodium), J. Biol. Chem. **87**:33-35, 1930.

Hydrogen ion concentrations were always measured with the Beckman vacuum tube p_H meter using glass and calomel electrodes. In some experiments daily readings were taken to determine the p_H changes in the bouillon. In other experiments greater intervals of time elapsed between readings. The frequent readings were necessary, as often a change in the p_H value occurred rather suddenly. This was especially important when the change from an acid to a more alkaline p_H occurred. This will be seen in the experiments to be a critical phase in the formation of skin test principle.

The experiments were begun in 1938. About fifty series of experiments were studied. More than 350 fractions were taken in order to determine the relation between changes in the hydrogen ion concentration and the formation and concentration of skin test principle. The desensitizing factor was studied in a much smaller number of fractions.

For the determination of the skin test factor, fractions were tested on from 5 to 30 patients. The concentration of skin test principle was compared with that in Lederle 1 : 30 trichophytin as a standard. Because we were often dealing with patients exhibiting marked sensitivity to trichophytin it was necessary to test a limited number of fractions on each person. However, as many as 12 fractions have been tested simultaneously in the same patient in a number of instances.

The concentration of skin test factor in the fractions was expressed in terms of the degree of the reaction following an intradermal injection of 0.1 cc. of Lederle 1 : 30 trichophytin.

Preparation of Trichophytin Fractions.—The pellicle was not used in this study, since it has been previously shown that there was no fluctuation of skin test principle in it.[2]

Material for study was pipetted off from the bouillon and passed through a Seitz filter, and enough merthiolate was added to make a final concentration of 1 : 10,000. This changed the final p_H of the fraction. However, we have established by many experiments that change in the p_H over a wide range of hydrogen ion values after the fraction was removed from the bouillon had no influence on the trichophytin reaction. Mediums alone varying in p_H from 4.0 to 10.0 did not give primary nonspecific reactions other than those which might be due to sensitivity to the original ingredients. This was rarely met with.

Reading of the Reaction.—In a few instances we were confronted with trichophytin fractions which were primarily toxic. Such fractions were met with when we used human blood plasma as buffering agents.

One-tenth cubic centimeter of the fraction to be tested was injected intradermally, usually on the extensor surface of the forearm, and the reactions were graded in the manner suggested by Lewis and Hopper.[7]

7. Lewis and Hopper,[9] p. 240.

In the charts given in this report the skin test factor is designated by the letter S. S_0 indicates an absence of skin test factor; S_1 indicates the same concentration of skin test factor as Lederle 1 : 30 trichophytin, and S_2 roughly indicates twice this concentration. A fraction was said to have an S_2 concentration of skin test principle if it produced an average reaction which was twice as great as that produced by an equivalent amount of Lederle 1 : 30 trichophytin.

RESULTS

EXPERIMENT 1.—*The Relation of the Hydrogen Ion Concentration to the Presence and Concentration of the Skin Test Factor.*—A. Changes of the Hydrogen Ion Concentration in Sabouraud's Bouillon with a

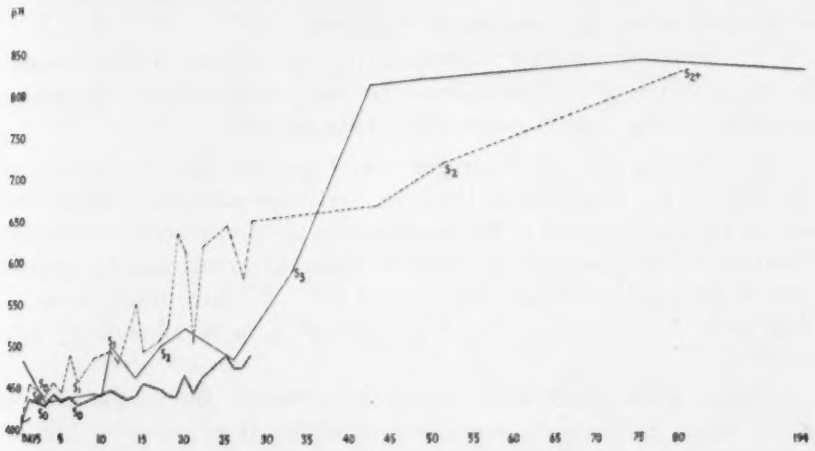

Fig. 1.—The relation of the hydrogen ion concentration to the presence and concentration of skin test factor. With a rise in the p_H the skin test factor begins to appear, and its concentration is roughly parallel to the rise in p_H. The solid line indicates series 26, p_H 4.83, no buffer. The dash line indicates series 2, p_H 4.0, no buffer. The solid line with dots indicates series 2, p_H 4.0, plus buffer.

Starting p_H of Approximately 4.0: It was seen (fig. 1) that when the hydrogen ion concentration was initiated at a p_H of approximately 4.0 to 5.0 there was a rise in the p_H value from the beginning or there was a slight initial drop, especially in the medium initiated nearer 5.0. It is important to note that although there was some up and down fluctuation in the p_H values the trend gradually rose toward the alkaline side. In nearly all instances at about the eightieth day the same p_H value was reached, approximately 8.5. The fluctuation in the p_H values was much greater in the medium without buffers, and it was seen that alkalinization also was much more rapid for the same period when there was no buffer in the medium.

The three day fraction from series 2 with buffer had no skin test factor. A seven day fraction from the same culture also contained no skin test factor, and at that time there was practically no rise in the hydrogen ion concentration. On the other hand, a seven day fraction from the parallel series of flasks which did not contain buffer, and which showed an appreciable rise in the hydrogen ion concentration, already contained as much skin test factor as the Lederle trichophytin.

The graph for series 26 indicates that with the rise in hydrogen ion concentration skin test factor began to appear and that there is a definite relation between the rise in the hydrogen ion values and the increased concentration of the skin test principle. This parallelism between the rise in the p_H value and the increase in the concentration of the skin test factor was still maintained as the culture became older, but it was not as striking as in the first few weeks of growth.

The curves on the charts indicate a trend rather than absolute changes in the p_H values. No doubt if more frequent readings had been taken a more fluctuating type of curve might have resulted.

B. Changes in the Hydrogen Ion Concentration of Sabouraud's Bouillon as It Is Commonly Used for the Preparation of Trichophytin: As we have pointed out in the discussion of the preparation of mediums, Sabouraud's bouillon as it is ordinarily made for culture and for preparation of trichophytin usually has a p_H of 6.5. We have found, however, that with the same methods of preparation a more alkaline p_H often resulted.

Figure 2 illustrates what may occur to the p_H and to the skin test factor when Sabouraud's bouillon with an initial p_H value of 6.68 and 7.08 is inoculated with T. gypseum. The graph for series 9 is a typical example of what was seen to occur in the great majority of instances. There was a rise in the p_H value from 6.68 until a maximum of 8.6 was reached. The rise may be rather abrupt or it may be gradual.

A fraction taken from series 9 on the seventh day showed a change in the p_H from 6.68 to 7.9. There was enough skin test factor present even at that early date to give twice the reaction of that of an equivalent amount of the Lederle trichophytin. However, not until there was an appreciable rise of the hydrogen ion concentration, by the forty-third day, was there a further demonstrable increase in the concentration of the skin test principle.

The solid line (series 26 and 27) in figure 2 illustrates what may sometimes occur, especially when the Sabouraud bouillon has a p_H above 7.0. The hydrogen ion concentration dropped. By the eleventh day it had decreased from 7.08 to 4.5. No skin test principle was demonstrated in the fraction taken at that time. Shortly after this period the tide turned toward the alkaline side. A fraction taken on the seventeenth

day, when the hydrogen ion concentration had risen from 4.5 to 5.63, had enough skin test principle to give twice the cutaneous reaction of the same quantity or the Lederle trichophytin. With the further rise in the hydrogen ion values the concentration of the skin test principle was increased.

C. Initiation of Sabouraud's Medium on the Alkaline Side with a p_H of Approximately 9.0: During the course of our experiments, since it was first noted that the skin test factor tended not to appear when the hydrogen ion value decreased, we attempted to initiate experimental conditions under which this phenomenon could be controlled at will. Early in our work we found it difficult to control the experimental conditions so that there would always be a slow but constant drop of the

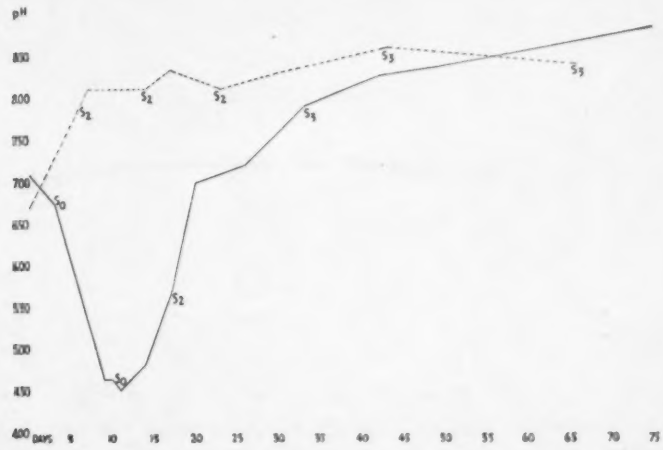

Fig. 2.—When Sabouraud's bouillon was initiated at a p_H of 6.68 and inoculated with T. gypseum, the p_H rose and skin test factor began to appear. When the bouillon was initiated at a p_H of 7.08 (on the alkaline side) the p_H dropped, and not until the p_H had begun to rise again was any skin test factor formed. The solid line indicates series 26 and 27, Sabouraud control medium, p_H 7.08. The dash line indicates series 9, Sabouraud bouillon, p_H 6.68.

hydrogen ion values and a correspondingly slow rise. If the changes were too rapid, fractions would have had to be taken at short intervals in order that the critical phase of the experiment, which was at the lowest point of the curve, would not be missed, and as a result the fractions would have been too numerous to test.

It was found that the addition of a 1:15 solution of phosphate (McIlvaine's) buffers in Sabouraud's bouillon and initiation of the hydrogen ion concentration between 8.6 and 10.0 gave us the most ideal conditions. Figures 3 to 7 graphically summarize the results of the experiments.

In figure 3 (series 19) the hydrogen ion concentration was adjusted at the extreme upper limits of alkalinity at which T. gypseum would still grow; this was at a p_H of about 11.0. It was seen that there was a spontaneous readjustment of the hydrogen ion concentration in about fifteen days to a p_H of approximately 9.0. The control flask, which was not inoculated with the organism, showed almost no further change in the p_H. The inoculated medium continued to show a slow drop until it had reached a p_H of 7.83 in sixty-eight days. After that it rose again, slowly, to a p_H of 8.94 at the end of one hundred and fifty-four days. Fractions taken the fifteenth and thirty-third days showed no skin-reactive principle. A fraction taken the one hundred and fifty-fourth day was seen to contain skin test principle.

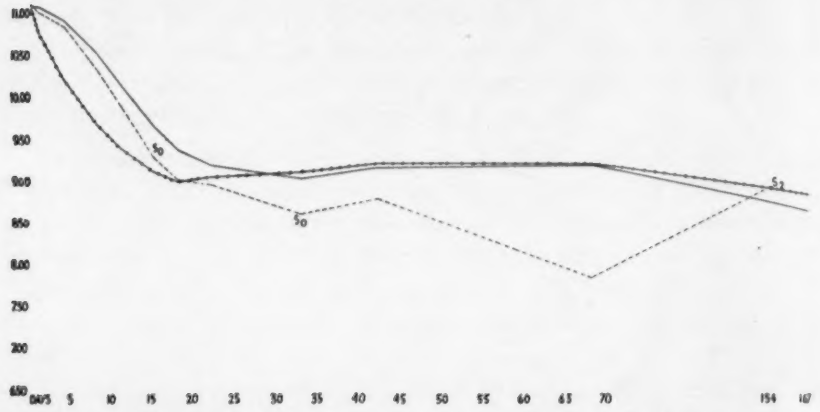

Fig. 3.—Sabouraud's bouillon initiated at a p_H of about 11.0 with and without phosphate buffer shows a spontaneous drop in the hydrogen ion values to about 9.0. The p_H of the bouillon inoculated with T. gypseum continues to drop below 9.0. No skin test factor was formed while the p_H was dropping. The solid line indicates series 19, p_H 11.08, plus buffer (not inoculated). The dash line indicates series 19, p_H 11.09, plus buffer (inoculated). The solid line with dots indicates series 19, p_H 11.05, no buffer (not inoculated).

Figure 4 shows the changes in the hydrogen ion values in series 27. The mediums were initiated at a p_H of 8.39 without buffer and 8.27 with buffer. Sabouraud's control medium for this experiment had an initial p_H of 7.08. The hydrogen ion concentration in all three mediums showed a rapid drop to a p_H below 5.0. The lowest value was attained by the bouillon without buffer, which in seventeen days had a p_H of 4.33. The swing toward the alkaline side was first demonstrated in Sabouraud's control medium, next in the bouillon without buffer and finally in that with buffer. Once the tide had turned it was most rapid in the same order. At the end of one hundred and ninety-four days they had all reached a p_H of approximately 8.5.

Fractions were taken on the third, eleventh, seventeenth, thirty-third and forty-ninth days. In Sabouraud's bouillon with buffer no demonstrable skin test factor was found in seventeen days, when the p_H value had reached its lowest point. Minimal quantities then began to appear at about thirty-three days. It can be seen that the p_H value had risen only slightly. The Sabouraud control medium, which was the same one as that used for series 26 (fig. 2), was tested simultaneously and demonstrated in a striking manner the lack of formation of the skin test principle while the p_H was dropping toward the acid side. It can be seen that the skin test principle rapidly appeared when there was a turn toward a more alkaline p_H. In the medium without buffer a moderate amount of skin-reactive factor could be demonstrated in the first eleven

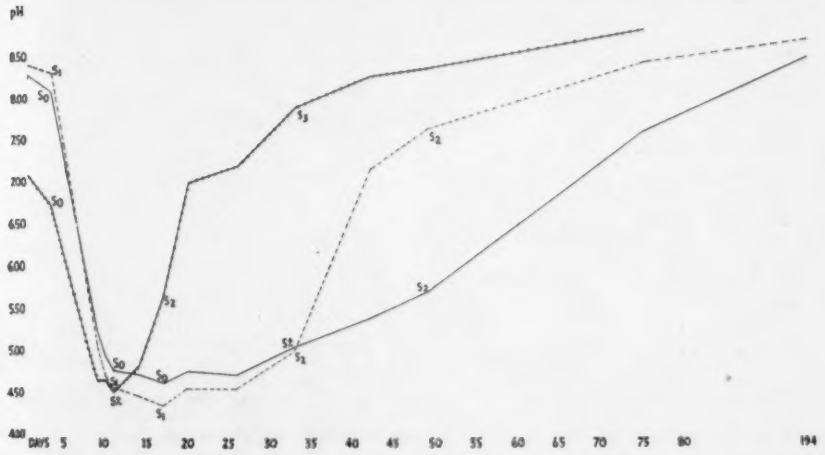

Fig. 4.—Sabouraud's bouillon initiated at a p_H above 7.0 with and without phosphate buffer and inoculated with T. gypseum. When phosphate buffer is added the p_H drops and no skin test factor is formed. Apparently some skin test factor is formed even though the p_H seems to be dropping when phosphate buffer is not present. There is a rapid increase in the concentration of this factor, however, when the p_H begins to rise. The solid line indicates series 27, p_H 8.27, plus buffer. The dash line indicates series 27, p_H 8.39, no buffer. The solid line with dots indicates series 26 and 27, Sabouraud control bouillon.

days of growth even though the p_H was apparently dropping. As the p_H rose, the concentration of the skin test factor showed a decided increase.

As will be seen from other experiments, a moderate amount of skin test factor would sometimes be formed although the p_H was dropping. It was only in the bouillon with phosphate buffer that we could predict with a fair degree of certainty that no skin test factor would be formed as long as the hydrogen ion concentration inclined toward the acid side. A possible explanation for this might lie in the observation that up and

down fluctuations tended to occur more frequently in nonbuffered bouillon. Such a slight up and down fluctuation might have been demonstrable in the nonbuffered medium had we determined p_H values more frequently.

Figure 5 (series 25) illustrates an experiment in which the medium was brought to a p_H of 8.88 with a 1:10 dilution of phosphate buffer. There was practically no change in the p_H values of the uninoculated control. The inoculated medium showed a marked drop in the p_H during the first sixteen days, and after some fluctuation this was followed by a decided rise. This was followed by a gradual drop until the final day of observation (ninety-one days). No skin test factor could be

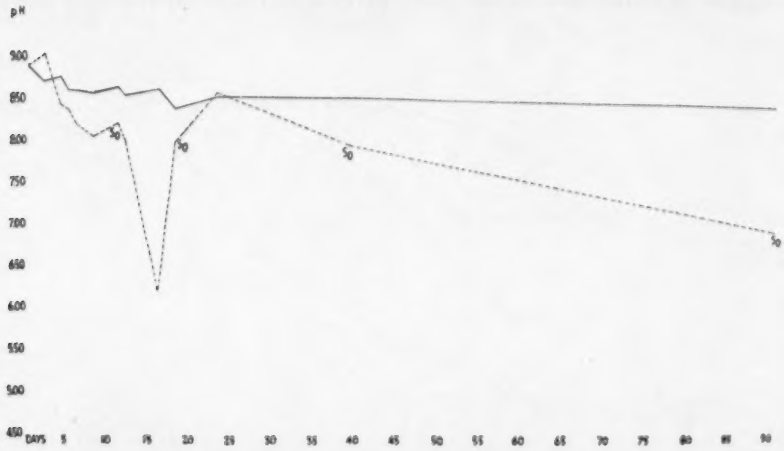

Fig. 5.—Instead of the usual 1:5 concentration of phosphate buffer, a 1:10 concentration was added to Sabouraud's bouillon. The solid line indicates series 25, p_H 8.88 (not inoculated), and shows little, if any, fluctuation in p_H. The dash line indicates series 25, p_H 8.89, and shows the changes in the p_H value after inoculation with T. gypseum. Apparently no skin test factor was formed.

demonstrated in fractions taken on the eleventh, eighteenth, thirty-ninth and ninety-first days.

Figure 6 is used to illustrate series 37 because the material taken on the twenty-second day was used for the desensitization experiments (experiment 5). The bouillon was initiated at a p_H of 8.6 with the addition of 1:5 phosphate buffer. On the twenty-second day the p_H was 7.72. No skin test factor could be demonstrated after intradermal injection in suitable patients.

EXPERIMENT 2.—*The Effect of the Type of Buffer on the Production of Skin Test Factor.*—It was thought that it would be of interest to study the effects of other buffers on the changes in the hydrogen ion concentration caused by T. gypseum and on the production of skin test factor.

A. Pooled Human Plasma: In a series of experiments pooled human plasma was added to Sabouraud's bouillon so that its final concentration was 50 per cent. In previous experiments it had been found that this served as a good culture medium for T. gypseum.[8] Any inhibitory effects which individual blood plasma might have were diluted out by pooling various blood plasmas.

Figure 7 (series 12) illustrates the changes in the hydrogen ion concentration when such a bouillon was acidified to a p_H of 4.58 with buffer and 4.72 without buffer. The Sabouraud control medium for this experiment had a p_H value of 6.58. It behaved in the usual way with a gradual rise in the p_H value. The plasma bouillon with buffer and that without buffer acted practically alike, at least for the first thirty days. They both showed a rather rapid rise, after a slight initial drop,

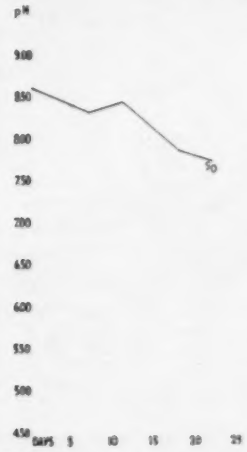

Fig. 6.—No skin test factor was formed while the p_H was dropping. The line indicates series 37, p_H 8.6, plus buffer. The fraction taken on the twenty-second day was used in the desensitization experiments.

to a p_H above 8.0. The plasma bouillon without buffer was followed much longer, and after fifty days the p_H began to show a gradual drop, going to 7.5 in two hundred and twenty-four days. Fractions were taken on the fourth and twentieth days. There was again an increase of skin test factor coincidental with the rise in the p_H value. The control flask, which was not inoculated, showed practically no change in hydrogen ion concentration.

In another experiment bouillon containing 90 and 50 per cent plasma was made. No additional buffers were added. The p_H of the 50 per cent plasma bouillon was 7.8 and of the 90 per cent plasma bouillon

8. Peck, S. M.; Rosenfeld, H., and Glick, A.: Fungistatic Power of Blood Serum, Arch. Dermat. & Syph. **42**:426 (Sept.) 1940.

8.28. Since the initial p_H of the Sabouraud bouillon before plasma was added was 7.16, it was seen that the pooled plasma alkalinized the medium. Figure 8 (series 11) shows that the p_H dropped in both bouillons to below 5.0. It dropped lower in the bouillon with 50 per cent plasma than in that with 90 per cent plasma. There was then a gradual rise in both, the rise being more abrupt in the 50 per cent plasma bouillon. As was previously noted, when the Sabouraud control medium was initiated above 7.0 it also dropped at first to a little above 5.6 before gradually rising again.

Fractions did not show nonspecific reactions, as has sometimes been found when pooled plasma was used in the medium. The nineteen day fraction from both showed an appreciable amount of skin test factor,

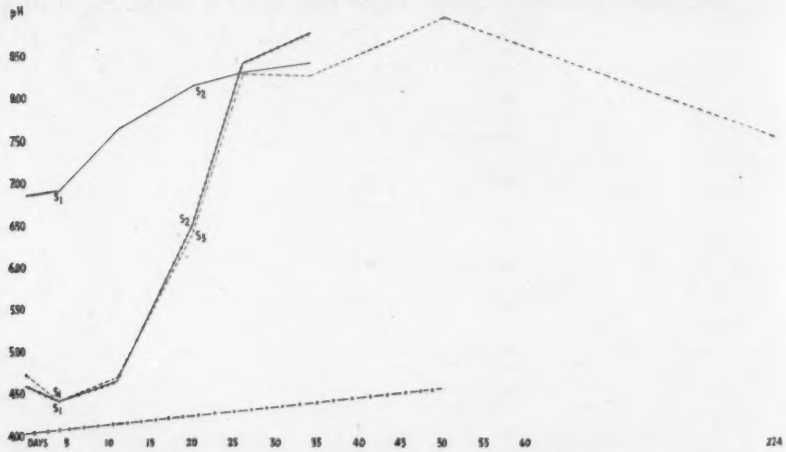

Fig. 7.—The addition of pooled plasma to Sabouraud's bouillon did not interfere with the formation of skin test factor, which roughly paralleled the rise in the p_H value. The solid line indicates series 12, Sabouraud's control bouillon. The dash line indicates series 12, p_H 4.72, no buffer, 50 per cent plasma (inoculated). The solid line with dots indicates series 12, p_H 4.58, plus buffer, 50 per cent plasma (inoculated). The dash line with circles indicates series 12, p_H 4.02, no buffer, 50 per cent plasma (not inoculated).

with much more in the 50 per cent plasma bouillon. The skin test factor apparently had been formed in spite of only a slight increase in the hydrogen ion concentration. In thirty-two days the concentration of the skin test factor had further increased, being greatest in the 50 per cent plasma bouillon, which showed the greatest rise in p_H value.

This again illustrates the fact that only with the phosphate buffer could we predict with certainty that a marked drop in the p_H value indicated the formation of little skin test factor. The control bouillon behaved in the usual way.

B. Barbital as a Buffering Agent: Barbital instead of phosphates was used in series 6 A as a buffer, according to the method previously

described. One batch of medium was initiated at a p_H of 5.11 and another at a p_H of 8.59. After inoculation with T. gypseum there was a steady rise in the acid bouillon (fig. 9) until in fifty-three days, a p_H of 8.63 had been reached. The p_H of the bouillon initiated on the

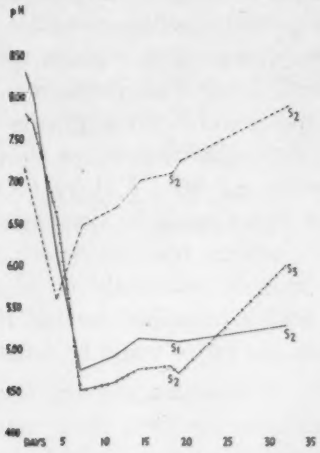

Fig. 8.—A p_H above 7.5 was produced by the addition of 50 and 90 per cent pooled plasma to Sabouraud's bouillon (series 11). Again it is seen that the formation of skin test factor roughly paralleled the rise in p_H values. The solid line indicates 90 per cent plasma bouillon. The dash line indicates Sabouraud control bouillon. The solid line with dots indicates 50 per cent plasma bouillon.

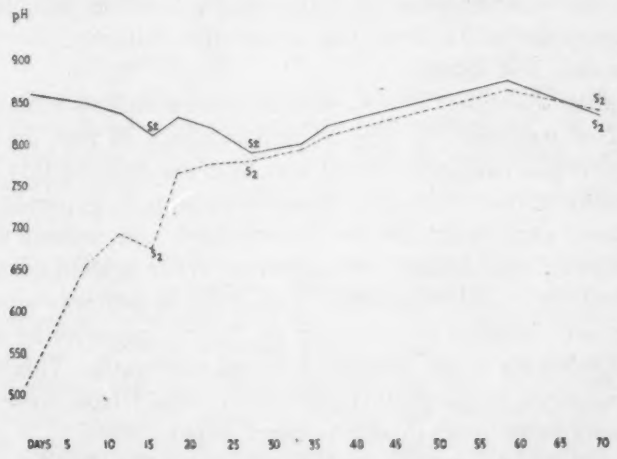

Fig. 9.—While the p_H was dropping (barbital used as a buffer) practically no skin test factor was formed. With a rise in the p_H, skin test factor began to appear. A fraction taken on the fifteenth day shows considerable concentration of skin test principle in the bouillon in which there was a decided rise in the p_H and practically none in the bouillon in which the p_H was dropping (series 6 A). The solid line indicates p_H 8.59. The dash line indicates p_H 5.11.

alkaline side gradually dropped to 7.9, in twenty-seven days, and then rose to 8.75, in fifty-eight days, practically paralleling the acid medium after it had reached its lowest point.

Fractions were taken on the fifteenth, twenty-seventh and sixty-ninth days. Barbital buffer in Sabouraud's medium, uninoculated, was used as a control. Nonspecific reactions were not demonstrated. There was not a single instance of a positive reaction with any of the fractions when a reaction to Lederle 1 : 30 trichophytin was negative. Practically no skin-reactive factor was found in the originally alkaline bouillon when the p_H was dropping. At the same time, on the fifteenth day, the acid bouillon showed a rise in p_H from 5.11 to 6.75, and an appreciable amount of skin-reactive factor could be demonstrated. By the twenty-seventh day the alkaline plasma bouillon, which had not yet shown an appreciable rise, still showed practically no skin-reactive factor. In sixty-nine days, when both batches had reached the same p_H, about 8.4, the same amount of skin test factor could be demonstrated in both.

EXPERIMENT 3.—*T. Purpureum and the Development of the Skin Test Principle.*—It has been observed on a number of occasions that patients with T. purpureum infections usually had a negative reaction to a trichophytin test. On the other hand, it has been pointed out by Lewis and Hopper,[9] as well as by others, that skin tests with a trichophytin made from T. purpureum cultures gave positive reactions in patients demonstrating sensitivity to other trichophytins. For this reason it was thought that it would be of interest to study the changes in the hydrogen ion concentration in Sabouraud's bouillon inoculated with T. purpureum and at the same time to note the relation of the changes in p_H to the skin test factor.

Sabouraud's bouillon at a p_H of 6.63 was inoculated with a recently isolated T. purpureum. It may be seen in figure 10 that the hydrogen ion concentration rose in the usual way to above 8.0 and that the curve seems similar to that found after inoculation with T. gypseum.

Fractions were taken on the twenty-third and seventy-fifth days. Skin test factor was formed, the maximum concentration of which was equal to Lederle 1 : 30 trichophytin. This was less than was usually found in Sabouraud's bouillon inoculated with T. gypseum with an equivalent rise in p_H value for about the same interval of growth. This may be of some significance, although this experiment would have to be repeated a great many times to see if such an effect were constant.

EXPERIMENT 4.—*The Total Nitrogen Content as an Index of the Concentration of Skin Test Factor.*—The total nitrogen content was determined in six fractions by the micro-Kjeldahl method. One three

9. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, Chicago, The Year Book Publishers, Inc., 1939.

day fraction, four thirty-three day fractions and one forty-nine day fraction were chosen. It can be seen in table 2 that the total nitrogen content bears absolutely no relation to the concentration of skin test factor.

EXPERIMENT 5.—*Attempts at Desensitization with a Trichophytin Fraction Which Apparently Had Little or No Skin Test Principle (350 A).*—The material for desensitization was taken from series 37 (fig. 6). Sabouraud's medium was initiated at 8.6 with the addition of 1:5 phosphate buffer, according to method 2. By the twenty-second day the p_H had dropped to 7.72. In routine testing in comparison with the Lederle trichophytin no skin test factor could be demonstrated.

Desensitization was attempted in 15 cases. In many of them fungi could be demonstrated directly or by cultures. In 1 case T. purpureum

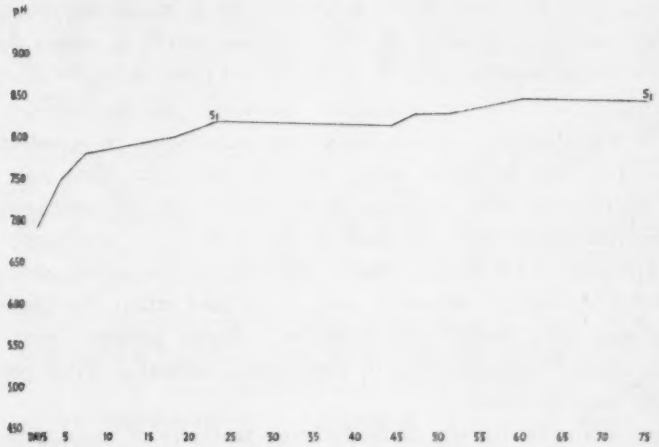

Fig. 10.—In Sabouraud's bouillon (series 16), with an initial p_H of 6.63, inoculated with T. purpureum, the skin test factor was formed but was less than that found after inoculation with T. gypseum with an equivalent rise of p_H for about the same interval of growth.

TABLE 2.—*Relation of the Concentration of Skin Test Factor in Trichophytin to the Total Nitrogen Content*

Figure	Series	Number of Days	Description of Specimen (Bouillon)	Total Nitrogen, Mg. per Cc.	Skin Test Factor, Concentration
1	26	33	p_H 4.83, no buffer	1.26	Three times that in Lederle 1:30 trichophytin
2 and 4	27	33	Plain Sabouraud bouillon	0.81	Three times that in Lederle 1:30 trichophytin
4	27	33	p_H 8.39, no buffer	1.16	Two times that in Lederle 1:30 trichophytin
4	27	3	p_H 8.27, plus buffer	1.24	None demonstrable
4	27	33	p_H 8.27, plus buffer	1.26	Practically none
4	27	49	p_H 8.27, plus buffer	1.27	Two times that in Lederle 1:30 trichophytin

was isolated. All of the patients had a positive reaction to Lederle trichophytin and a negative reaction to the twenty-two day fraction from series 37 (350 A).

At this time no attempts will be made to evaluate any results other than the effects on the trichophytin test.

About one half of the subjects had a 1 to 2 plus reaction, and the others showed a 3 to 4 plus reaction. Several methods of desensitization were attempted. The trichophytin was given subcutaneously. In some instances the initial dose was 0.3 or 0.4 cc. with an increase by 0.1 cc. at each subsequent injection until about 1 cc. was given, which dose was maintained. In other cases the initial dose was 1 cc. and the amount was not increased at each subsequent injection. In another group 2 cc. was given as the initial dose without any further increase. The injections were given two or three times a week. In 2 instances there was a moderate reaction, consisting of erythema and swelling, when 2 cc. was used as the initial dose for patients with a 3 to 4 plus trichophytin reaction.

Desensitization was accomplished in nearly all instances. It was usually brought about in from six to ten injections, in some instances in as short a time as three weeks and in others in from four to five weeks. In patients with strongly positive trichophytin reactions a more rapid desensitization was achieved when 1 or 2 cc. was used for the initial injections. Of course, the desensitization required much fewer injections when larger amounts were used and when the trichophytin reaction was only moderately positive. Even patients with 4 plus reactions could be desensitized in three weeks when 2 cc. of the 350 A was given twice a week.

It seems that by the use of fairly large amounts of this fraction rapid desensitization was possible with practically no local reactions except in the 2 subjects with the strongly positive trichophytin reactions. No focal reactions were observed. In 2 instances complete desensitization was not obtained. One of the patients had a 2 plus reaction to the Lederle trichophytin and a negative reaction to the fraction when desensitization was initiated. He was given 1 cc. once a week for ten injections. At the end of that time there was still a plus-minus reaction to the Lederle trichophytin. The other patient had a 2 plus reaction at the start of the experiment. One cubic centimeter of the fraction was given every five days for twelve injections with no desensitization.

We believe that the following case deserves a more detailed description:

D. G., aged 12, had been observed by one of us (S. P.) since Dec. 21, 1940. There was a dermatophytosis of both feet, and T. gypseum was isolated from the lesions. Under antiparasitic treatment he was clinically cured after a few weeks. He returned on March 19 with a recurrence on the feet and the beginning of a vesicular eruption on the hands. The injection of Lederle 1:30 trichophytin

gave a 3 plus reaction, and 350 A gave a negative reaction. He was given the following amounts of 350 A: March 20, 0.5 cc.; March 21, 1 cc.; March 22, 1.5 cc., and March 24, 2 cc. He was retested on March 24 with the Lederle trichophytin, and the reaction was 1 to 2 plus. The injection of 2 cc. of 350 A caused a moderate local redness without swelling. On March 26 and 28, 2 cc. was again injected, and retesting on the last date showed a 1 plus reaction to the Lederle trichophytin. The clinical improvement was noteworthy.

EXPERIMENT 6.—*Is Skin Test Factor Present in the Fractions Which Failed to Give a Positive Reaction in Sensitive Patients?*—In the previous experiment it was pointed out that on several occasions the injection of larger amounts of so-called skin test–free fractions produced some erythema and swelling in those patients who were decidedly sensitive to the Lederle trichophytin. This led us to conceive of the possibility that skin test principle in minimal amounts might have been present in these fractions.

In order to investigate this possibility, a seventeen day fraction (238 from series 27) and a twenty-two day fraction (350 A from series 37), in which no skin test factors were demonstrated, a thirty-three day fraction from a bouillon known to have a great deal of skin test factor, plain Sabouraud bouillon, not inoculated, to which 1 : 10,000 merthiolate was added and Sabouraud bouillon, also not inoculated, the p_H of which was brought to 8.97 with a buffer and to which 1 : 10,000 merthiolate added were evaporated to one tenth of their original volume in an oven at a temperature of 120 C.

All of these solutions were then tested in 6 patients. Two of the patients who gave a negative reaction to Lederle trichophytin also gave a negative reaction after intradermal injections of the concentrated solutions. As was expected, the material known to contain skin test factor produced increased cutaneous reactions when compared with the original unconcentrated material. Fraction 350 A injected after concentration in 3 of the patients who showed a 2 plus reaction to Lederle trichophytin showed in 2 of them a plus-minus reaction and in 1 a 1 plus reaction. Another patient who had a 1 plus reaction to Lederle trichophytin gave a negative reaction to the concentrated 350 A. Fraction 238 showed comparatively greater reactions after concentration than 350 A but much less than that given by Lederle trichophytin.

From this experiment we can deduce that even those fractions which apparently gave negative reactions to trichophytin tests did have small amounts of skin test principle. However, even after ten times concentration, the amount was less than that found in Lederle 1 : 30 trichophytin.

COMMENT

It seems to have been adequately proved in our experiments that there is a relation between the changes in the hydrogen ion concentra-

tion in Sabouraud's bouillon and the appearance and quantity of the skin test factor. The fact that a drop in p_H value was indicative of that period when this principle either was not formed or was present in minimal amounts might be of practical importance.

The chief reason given for the initiation of Sabouraud's medium at a p_H of 6.5 for the standard preparation of trichophytin was to make the occurrence of contamination less likely. From our experiments a further basis for not initiating Sabouraud's bouillon on the alkaline side seems to have been established. It may result in a drop in the p_H value in the bouillon during the first period of growth, with a resulting nonappearance of the skin test principle. As far as the ordinary preparation of trichophytin is concerned, this factor is practically eliminated because it is usual to allow growth to continue for six weeks or longer. By that time a rise in the p_H value has already occurred and with it the formation of skin test principle. In addition, since both the pellicle and the bouillon are usually used in the manufacture of trichophytin, enough skin test principle is always present in the pellicle to make up for any lack in the bouillon.

It seems, however, that our experiments form the basis for the preparation of trichophytin by a more practical and rapid method.

Culture mediums should be initiated at a p_H between 4.5 and 5.0. In a medium with such an initial p_H value skin test factor is rapidly formed. It is necessary only to determine the p_H value from time to time. Once a rise in several degrees of p_H is found, there is almost certain to be a parallel increase in the skin test factor. This was found to occur in as short a time as seven days. Such a trichophytin would be adequate for testing hypersensitivity to fungi. Because it is not necessary to use pellicle the whole procedure is simplified.

It has been shown that initiation of the medium on the alkaline side plus the addition of 1 : 5 phosphate buffers caused a drop in the p_H value of the medium. In such a preparation practically no skin test factor was formed in most instances. In spite of this, trichophytin prepared from this could be used for rapid desensitization in patients who were sensitive to trichophytin (skin test factor). This suggested but by no means proved that the desensitizing principle was apparently not identical with the skin test factor.

We do not believe that the demonstration of a small amount of skin test principle in our desensitizing material could serve as a basis of explanation for the rapid desensitization achieved in our cases. An equivalent amount of skin test factor as it is found in the Lederle trichophytin certainly would not give comparable results.

It would only be pure speculation to discuss why phosphate and barbital buffers bring about an initial drop in the hydrogen ion concen-

tration in Sabouraud's bouillon initiated on the alkaline side. In a number of experiments with apparently the same preparation of the medium, as far as the hydrogen ion concentration and buffers were concerned, even when the same strain of fungi was used we were unable to produce a consistent drop in the p_H with concomitant lack of formation of skin test principle. We were led to believe that the difficulty lay either in the strain of fungi or perhaps in the peptone which was used. It would be of great practical importance if all of the factors which were necessary to bring about a drop toward the acid side were known. A great deal of material and time was lost in attempting to prepare desensitizing material which was lacking in skin test principle because such knowledge was lacking.

It was not practical to use blood plasma as a buffering agent because we often found primarily toxic reactions with such trichophytins. Barbital could not be used because of the possible complications from the drug itself.

It might be of significance, for the explanation of the lack of trichophytin hypersensitivity in the average patient with T. purpureum infections, to note that that organism formed relatively less skin test factor in Sabouraud's bouillon than T. gypseum did under similar conditions for the same time.

Many authors have attempted to use the total nitrogen content as a measure of standardization of trichophytin. It is seen from experiment 4 (table 2) that there was apparently no relation between the nitrogen content of bouillon and the concentration of the skin test factor.

A more practical method for treatment seemed to have been developed by the use of our desensitizing material which contained practically no skin test factor. Because of the presence of the small amount of skin test factor, there was still a theoretic possibility that, as small as this quantity was, it still might play some role in desensitization. In order to prove that the skin test factor and the desensitizing principle are not identical, proper chemical studies and identification would have to be made. If it could be shown that the one was a carbohydrate or a polysaccharide and the other a protein, the controversy would be brought much nearer solution and the proper standardization of trichophytin could be attempted.

SUMMARY AND CONCLUSIONS

1. When Sabouraud's bouillon was acidified with hydrochloric acid or phosphate (McIlvaine's) buffers and inoculated with T. gypseum, there was a rise in p_H. In approximately seventy-five to eighty days it attained a p_H of 8.6, and after that time it remained relatively unchanged. With the rise in the p_H value the skin test principle began to appear, and within limits its concentration roughly paralleled the rise

in the hydrogen ion concentration. A rise in the p_H from 4.0 to 6.0, even if it occurred in a relatively short time, usually indicated a concentration of skin test principle which was in excess of that found in an equivalent amount of Lederle 1 : 30 trichophytin.

2. When Sabouraud's bouillon was initiated on the alkaline side by the addition of 1 : 5 phosphate buffers, at a p_H of 9.0 or 10.0 or even somewhat lower, and inoculated with T. gypseum, the hydrogen ion concentration usually dropped to below 5.0 before it increased again. Finally, a p_H of about 8.6 was attained with little further fluctuation. While the p_H was dropping the skin test principle was formed in minimal quantities or not at all. It became manifest again as the p_H began to rise, and its concentration here also was roughly parallel to the rise in the p_H value.

3. Pooled plasma and barbital were also used as buffers. When pooled plasma was used as the buffer some skin test principle was formed even though the p_H dropped. The barbital buffers acted similar to the phosphate buffers, as far as their influence on the formation of skin test factor was concerned.

4. T. purpureum formed less skin test principal than T. gypseum under the same experimental conditions.

5. The total nitrogen content of trichophytin was found to bear no relation to the amount of skin test factor present in bouillon.

6. We were able to prepare trichophytin fractions in which no skin test principle could be demonstrated even in persons who were strongly sensitive to the Lederle trichophytin. Such trichophytins were shown to be extremely effective in producing rapid desensitization in suitable patients without any local or focal reactions.

7. The experiments cited suggest that skin test factor is not necessarily identical with the desensitizing principle. Apparently some separation of one of these two factors has been accomplished.

RINGWORM OF THE FEET: SHOES AND SLIPPERS AS A SOURCE OF REINFECTION

FINAL REPORT

ROBERT C. JAMIESON, M.D.
AND
ADELIA McCREA, PH.D.
DETROIT

In presenting this completed study of shoes and slippers as a source of infection or reinfection in cases of ringworm of the feet, we have added a supplementary study of a small series of cases (25) in which we were interested in learning whether the organisms found in the shoes and on the skin were identical. Analysis of this series will follow the discussion of the main study.

When one considers the widespread prevalence of infections of the feet due to fungi that are considered to be pathogenic in man, it is only natural to expect to find these fungi in articles of clothing in intimate contact with the affected areas. It is also believed that the distribution of these organisms is as universal in the mycologic as in the bacterial field. Consequently the human foot would be in frequent contact with fungi, both pathogenic and nonpathogenic, which could probably be found at almost any time on the feet, especially between the toes, on the stockings and in shoes which had been worn for a few days or weeks.

In line with our works is the report of Berberian,[1] who investigated the ability of fungi to remain viable in stockings after simple laundering. Not only were fungi grown from washed stockings of infected persons but growth could be obtained after inoculation of cotton, silk or woolen hose with Trichophyton interdigitale. Cotton, linen and leather used as inner linings of shoes were also found to be good culture mediums for this fungus. Wood and seaweed proved to be good culture mediums, but the growth on rocks was less luxuriant.

Magee and Hartfiel[2] made some interesting observations on ringworm in two orphanages. Although they found an average incidence

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From the Research Laboratories of Parke, Davis & Co.

Read in a symposium on Superficial Fungous Infections at the Sixty-Fourth Annual Meeting of the American Dermatological Association, Inc., New Orleans, April 10, 1941.

1. Berberian, D. A.: Dermatophytosis of Feet: Sources and Methods of Prevention of Reinfection, Arch. Dermat. & Syph. **38**:367 (Sept.) 1938.

2. Magee, H. F., and Hartfiel, H. A.: Eradication of Ringworm of Feet in Two Orphanages: Control and Treatment, Arch. Pediat. **57**:48 (Jan.) 1940.

of clinical ringworm of 47 per cent, they found a group of young girls who were comparatively free of infection. This freedom they attributed to the fact that the girls had been going barefoot for a few weeks before being examined, the result being due to complete aeration and lack of retained heat and moisture. In girls of high school age, who wore shoes and stockings, the incidence was much greater. They also observed a case in which the condition was severe and could be traced to a pair of old, used (presumably infected) tennis shoes worn without socks. They reported excellent results from placing twice a day in the shoes and on the feet a powder composed of hydroxyquinoline, sodium perborate, sodium borate, boric acid and aluminum silicate.

The use of this powder would seem to be of great value in institutions, where the incidence would be high. Rein and Rosenblum [3] discovered the infection in 86 per cent of 600 male prisoners.

With this widespread distribution in mind one cannot help wondering at the blissful serenity of the public in repeatedly exposing themselves to infection by walking with unprotected feet at home, outdoors, in locker rooms and on bathing beaches. People do not employ even elementary methods of sanitation to prevent infection. Natural immunity must be the explanation for many persons never having had a fungous infection.

EXAMINATION OF SHOES FOR FUNGI

As the object of our study was the determination of the presence of pathogenic as well as of nonpathogenic fungi in the shoes worn by persons who clinically had dermatophytosis of the feet, the scrapings from the skin were examined in only a portion of this series but were examined in all cases of the second series.

The upper surface of the inner sole of the shoe in active use was curetted for scrapings, but in some instances both new and old shoes were examined.

With the exception of 2 patients with rather severe dermatophytosis, all the patients comprising this series had a mild dermatitis with recurring manifestations. All had lesions of the feet only and presented the usual criteria for clinical diagnosis of a ringworm infection. Two thirds of the patients of the entire series were males. The age limits were 4 and 66 years. Various types of occupation were represented.

Mycologic Technic.—No change was made in the mediums. Sabouraud's formulas, as given in detail previously,[4] were used throughout

3. Rein, C. R., and Rosenblum, M.: A Study of the Incidence of Foot Ringworm Among Prisoners, M. Rec. **145**:363 (May 5) 1937.

4. Jamieson, R. C., and McCrea, A.: Recurrence or Reinfection in Ringworm of the Hands and Feet, Arch. Dermat. & Syph. **25**:321 (Feb.) 1932.

this work. Up to midsummer of 1940 it was still possible to obtain from France the *peptone granulée Chassaing* of Sabouraud's medium. Thus all ingredients have remained unchanged in the course of these studies.

TABLE 1.—*Results of Examination of Shoes for Parasitic Fungi of the Skin*

Results of Culture	Number of Samples		
	Present Series	Previously Reported	Totals
Definitely positive	24	16	40
Definitely negative	12	13	25
Doubtful	11	23	34
Control (shoe of noninfected person)	0	1	1
	47	53	100

TABLE 2.—*Parasitic Fungi of the Skin Found on Examination of the Shoes*

Organisms Isolated	Number of Samples		
	Present Series	Previously Reported	Totals
Known pathogens			
Trichophyton: interdigitale 18			
violaceum 4	22	14	36
Microsporon	2	0	2
Epidermophyton	0	2	2
			40
Suspected pathogens			
Monilia	14	11	25
Torula (Cryptococcus)	2	4	6
Yeast	2	8	10
P. brevicaule	6	5	11
			52
Believed nonpathogenic:			
Aspergillus	30	43	73
Penicillium (other than P. brevicaule)	17	27	44
Alternaria	2	7	9
Hormodendron	1	1	2
Mucor	3	3	6
Macrosporon	0	4	4
Fusarium	0	2	2
Briarea	0	1	1
Hyalopus	0	1	1
			142

Results.—With the finding of organisms in 40 per cent of cases in this series and the results doubtful in 34 per cent, it appears that actual and probable infection of the inner soles of shoes is widespread. The organisms found in these shoes would presumably vary in number and variety according to the length of time the shoe had been worn during the course of the disease, the severity of the infection, the care and protection of the feet and the frequency of change of stockings.

T. interdigitale was found to be the most frequent invader, Trichophyton violaceum, Microsporon and Epidermophyton being present in only a few cases.

Among suspected pathogens Monilia was found in 25 instances, Torula, yeast and Penicillium brevicaule being found in the remaining 27. Although Monilia is here classed as a suspected pathogen, it is the belief of one of us (R. C. J.) that it is a true pathogen in cases which are clinically indistinguishable from those in which the condition is due to infection by Trichophyton but in which no other organism besides Monilia can be isolated.

It is also not improbable that certain fungi of the Aspergillus and Penicillium groups, usually considered nonpathogenic, are able to grow

TABLE 3.—*Analysis of Results of Cultural Study of Shoe Scrapings*

	Number of Samples		
	Present Series	Previously Reported	Total
Clinically positive	47	53	100
Clinically and culturally positive (pathogenic fungi)	24	16	40
Clinically positive (suspected pathogenic fungi in culture: Monilia, Cryptococcus, yeast and P. brevicaule)	24	28	52
Clinically positive and culturally negative (no pathogenic fungi)	12	16	28
Culturally negative (no pathogenic fungi-control)	0	1	..
Nonpathogenic fungi (with and without the pathogenic varieties)	53	89	142
Completely negative for all organisms (bacterial and fungous)	5	3	8
Trichophyton only in culture	7	1	8
Nonpathogenic fungi only	3	15	18
Specimens with multiple organisms of both pathogenic and nonpathogenic types	31	37	68

and cause clinical manifestations on the skin of a few persons. In 18 of the cases only nonpathogenic fungi were found in the scrapings from shoes but nonpathogenic fungi were found with and without pathogens in 142. In 68 of the cases multiple organisms of all types were found, while Trichophyton alone was found 8 times.

In a few instances discrepancies in cultural findings were inexplicable. In 1 case in which there were moderate clinical manifestations and a dermatophytid on the hands, no growth was obtained from scrapings of either new or old shoes. It is suggested (A. McC.) that this result was due to excessive alkalinity of the skin or material or to treatment preceding the time of sampling. Examination of scrapings of skin in 1 case of clinically positive dermatophytosis revealed many hyphae, but no growth resulted from culture. It is also possible that the location of the lesions and the minimum amount of scaling in some persons would account for negative cultures of scrapings from shoes.

SHOE-FOOT SERIES

Since cultural examination in the preceding series had revealed that 40 per cent of specimens examined harbored pathogenic fungi, we became interested in the question of whether the same pathogen could be found in the scrapings from the skin as well as from the soles of the shoes. In the cases of this series scrapings from the skin were examined culturally as well as micoscopically, the scrapings from shoes naturally being examined only by culture.

Technic.—The technic here was changed from the potassium hydroxide method of our preceding work to the procedure recommended by Cornbleet.[5] This has proved to give better results in clearing the tissue. The reagent dries quickly to form crystals, however; so the slides should be kept in Petri dishes during the period of digestion to prevent evaporation. Sodium sulfide crystals are dissolved with a few drops of water. This is added to an equal amount of alcohol (95 per cent), forming a cloudy precipitate. Distilled water is then added drop by drop until the precipitate redissolves and remains in solution. The reagent should be kept in a glass-stoppered bottle.

Results.—In a study of results of cultural examination of scrapings from skin and shoes it will be seen that accepted pathogens (Trichophyton, Microsporon and Epidermophyton) were found in the skin in 8 of the 25 cases but in the scrapings from shoes in only 12 cases. The smaller number of positive results in the shoes could be explained by differences in the care of the feet, frequency of change of stockings, degree of dermatophytic activity and age of the shoes.

In the 12 cases in which scrapings from shoes showed pathogens, the same organisms were found in cultures of scrapings from the skin of the corresponding feet. This would indicate that the insoles can presumably be contaminated from infected feet (66 per cent in this series), especially in view of a previous observation [6] that some new shoes which were examined showed little contamination and in some instances were sterile.

Of the possible pathogenic fungi which were found (Monilia, Actinomyces, Torula, yeast and P. brevicaule) the number isolated in scrapings from skin and shoes was equal, 20 and 21 respectively. Scrapings of the skin in only 2 instances yielded Monilia alone; in scrapings of the shoe Monilia was found 7 times in a total of 27 cases. Monilia was cultured 13 times from scrapings from the feet (52 per cent) and 14 times (56 per cent) from scrapings from shoes. However, in all but 2 of the 13 cases it was accompanied by a definite pathogen which of

5. Cornbleet, T.: A Reagent for Demonstrating Fungi in Skin Scrapings and Hair, J. A. M. A. **95**:1743 (Dec. 6) 1930.

6. Jamieson, R. C., and McCrea, A.: Shoes: A Source of Reinfection in Ringworm of the Feet, Arch. Dermat. & Syph. **35**:203 (Feb.) 1937.

itself could account for the infection. Judged by these and previous studies,[6] the status of Monilia appears to be secondary to that of the various species commonly grouped as dermatophytes. Although Monilia frequently complicates ringworm of the feet, it is probably less often than is commonly thought the only causative agent of cutaneous mycoses.

In addition to the accepted and possible pathogens, many varieties of accepted nonpathogenic organisms were revealed in culture (14

TABLE 4.—*Frequency of Isolation of Organisms from Scrapings of the Skin and Shoes*

Fungus	Skin Scrapings		Shoe Schapings	
	Number	Per Cent	Number	Per Cent
Trichophyton	12	48	8	32
Microsporon	5	20	4	16
Epidermophyton	1	4	0	0
Monilia	13	52	14	56
Aspergillus	7	28	23	92
Penicillium	4	16	5	20
Actinomyces	1	4	1	4
Torula ("red yeast")	1	4	0	0
Yeast	1	4	1	4
Fusarium	1	4	2	8
Alternaria	1	4	2	8
Rhizopus	1	4	0	0

TABLE 5.—*Analysis of Twenty-Five Cases Studied Culturally*

	Skin Scrapings	Shoe Scrapings
Accepted pathogens: Trichophyton, Microsporon, Epidermophyton	18	12
Possible pathogens: Monilia, Actinomyces, Torula, Yeast and P. brevicaule	20	21
Accepted nonpathogenic organisms	10	27

TABLE 6.—*Analysis of Twenty-Five Cases Studied Microscopically*

Dermatophytes present	18
Dermatophytes not present	7
Doubtful	0
Cases with same pathogens in skin and in shoe..	12

times in cultures of scrapings from the skin), while several varieties were found 31 times by culture of scrapings from shoes. This result seems rather natural if one considers the lack of care the shoe receives compared with that given the foot and the far greater opportunity for the development of contaminants of these groups.

The chief point of interest in table 4 is the finding of trichophyton in almost 50 per cent of scrapings from skin, the same organism being found in 32 per cent of scrapings from shoes.

This study reveals that a fairly large proportion of persons with fungous infections of the feet are able to contaminate the shoes they wear. It would, therefore, seem logical to conclude that such shoes if unsterilized are potential sources of reinfection to the original wearer, if he is fortunate enough to be completely cured of this infection, or may cause a new infection if worn by a person previously uninfected. It should be made a rule to sterilize all shoes and slippers (with formaldehyde or by other means) before they are used again or given away for use.

Although recurrences are the rule when the fungus is once thoroughly established in the skin of the feet and toes, these recurrences take place over varying periods during which many new shoes are worn but, in all probability, bedroom slippers are unchanged. If an actual reinfection occurred it would more likely be due to the slipper than to the shoe.

In 5 instances of the foot-shoe series, scrapings from slippers in use were examined culturally. In 4 of the 5 the same pathogenic fungi were found as those on the feet; 1 specimen was negative. In 1 instance in which only one foot was infected both slippers were examined; the slipper worn on the unaffected foot was culturally negative, whereas culture of material from the other slipper showed pathogens.

Although this report does not cover a large series we believe it is representative of a cross section of the population, embracing as it does persons of both sexes, all ages and many occupations.

We should like to endorse the recommendation of Berberian [1] that rubber slippers be used in gymnasiums and swimming pools as well as at bathing beaches in an attempt to reduce the possibility of infection. We might also add that these slippers should be frequently sterilized with formaldehyde gas.

The suggestion of Seldowitz [7] of incorporating in leather insoles the fungicide known as 8-hydroxyquinoline, parachlorometaxylenol and chlorthymol for eradication of ringworm of the feet might be extended to include all new shoes and slippers, thus preventing the insoles from becoming carriers of pathogenic fungi.

SUMMARY AND CONCLUSIONS

We have presented the results of a cultural study of scrapings from shoes in a group of cases of clinical dermatophytosis and have included the results of cultures made from the skin and shoes in a smaller series.

From this study it is definitely shown that footwear harbors pathogenic fungi and may be the potential source of reinfection for many persons and of primary infection for others.

7. Seldowitz, M.: Treatment of Dermatophytosis Pedis with Medicated Insoles, Arch. Dermat. & Syph. **42**:576 (Oct.) 1940.

We feel that prophylaxis should be more strongly emphasized for both infected and noninfected persons and that footwear should be sterilized at intervals during a course of treatment as well as at the conclusion of such treatment.

ABSTRACT OF DISCUSSION OF PAPERS IN SYMPOSIUM ON SUPERFICIAL FUNGOUS INFECTION

DR. GEORGE M. LEWIS, New York: This new trichophytin may or may not prove to be superior to the ones now in use. Drs. Miller, Stewart and Kimura have not made extravagant claims for the product; the obvious advantage which they pointed out is that it is a pure product. I believe that trichophytin has value in the diagnosis of fungous infections and should be used by investigators doing mycologic work; it should not replace microscopic or cultural methods of diagnosis, however. Trichophytin has come into some disrepute because of unwarranted claims made for it or because its limitations were not recognized.

In evaluating the product it is of interest to try to correlate the response to the administration of the extract with the infecting micro-organism. If one does that, one should be able to speak with some certainty regarding specific infections. For instance, as has been shown, in an inflammatory fungous infection in which, say, Trichophyton gypseum is the infecting micro-organism, there is a good possibility that the skin will become sensitized so that a reaction will be present after trichophytin is injected. In infections due to Trichophyton purpureum there are few reactions to trichophytin when the test is read after forty-eight hours. Drs. Miller, Stewart and Kimura mentioned the wheal reaction to trichophytin observed ten or fifteen minutes after the test. In my experience this phenomenon is seen only in the presence of infections due to T. purpureum, and in 50 per cent of such infections there is an immediate wheal reaction. When one observes the immediate wheal reaction, it is thus possible to postulate the type of fungus causing the infection. Regarding the therapeutic phase a word of caution is in order. The results have been so conservatively presented that I do not think any one can help but feel that this new trichophytin should be given a further trial. The disappointing results with other trichophytins, including the South American brand, lead one to withhold final judgment.

DR. H. J. TEMPLETON, Oakland, Calif.: Several years ago Dr. Krueger and I collaborated in the presentation of a short preliminary report on this subject (Krueger, A. P., and Templeton, H. J.: Preparation of Trichophytin, ARCH. DERMAT. & SYPH. **30**:9 [July] 1934). In order to use local organisms, Dr. Krueger obtained the dermatophytes in the clinic for students at the University of California. He furnished me with a supply of trichophytin, and I injected it into the forearm of each of a small series of patients, injecting into the opposite forearm Metz's trichophytin as a control. As far as I could see, the reactions were practically identical except that the reaction to the Krueger trichophytin was slightly more active. It would have been much better had I used as a control an orthodoxly prepared denatured trichophytin from the same organisms and of the same nitrogen content. It seems to me that the Krueger method of preparation of antigens is basically sound. It is well known that when various proteins are subjected to heat or chemicals, certain changes occasionally take place which tend to make them less antigenic. But with the Krueger method of preparation, with the ball mill, that danger is done away with.

I should also like to discuss the paper by Drs. Jamieson and McCrea. In 1928-1930 a committee composed of Dr. Legge, Dr. Bonar and myself studied the

problem of epidermomycosis at the University of California (Legge, R. T.; Bonar, L., and Templeton, H. J.: Epidermophytosis at the University of California, ARCH. DERMAT. & SYPH. **27**:12 [Jan.] 1933). Bonar and Dreyer (Bonar, L., and Dreyer, A. D.: Studies on Ringworm Funguses with Reference to Public Health Problems, *Am. J. Pub. Health* **22**:909 [Sept.] 1932) reported that various local dermatophytes could easily be grown on damp wool, damp silk, slimy wood and leather but could not be grown on damp cotton or dry wood. This was explained by the nitrogen requirements of the fungus; that is, cotton does not contain the nitrogen that the fungus requires, nor does dry wood, but the other materials, including shoe leather, do contain the natural growth requirements of the fungus. Moreover, the effect of laundering on fungi which may be found on or growing in socks was studied. There are certain standard laundry practices in the United States. When silk socks, wool socks and cotton socks are sent to the laundry, they are subjected to different temperatures in the laundering process. Cotton socks are heated above the thermal death points of the fungus, whereas one does not dare to heat silk and wool socks to that temperature because of shrinkage and deterioration. That is another reason for having patients with fungous infections wear cotton socks.

DR. EUGENE F. TRAUB, New York: I should like to comment on the presentation of Drs. Greenwood and Rockwood, which interested me because about two years ago I was given some floor covering containing a copper cement. It had been discovered rather accidentally that when this covering was cultured fungi were never found. After further experimentation this type of floor covering was recommended for locker rooms and other places where persons walking barefoot might acquire fungous infections. The work of Drs. Greenwood and Rockwood suggests that perhaps further checking should be done, because the agent that was supposed to be active was the copper. I do not know exactly what preparation of copper was used in the floor covering, but it was supposedly a copper solution in cement.

The question of treatment with biologic methods has also been interesting. Dr. Peck's work has been familiar to me for some time, because I thought that possibly his separation of a so-called skin-reactive factor and the therapeutic factor might be the answer to this problem. When I treated fungous infections, I desensitized the patients or hyposensitized them, but I found that this state lasted only a relatively short time, often only weeks to months. In a patient who has only a focal infection and not a dermatophytid, desensitizing should not be of any value unless one also immunizes the patient at the same time. In a patient with a dermatophytid, desensitization or hyposensitization might prove of some value, but unfortunately such a condition may clear up in a rather short time whether one gives injections of trichophytin, local treatment or no treatment at all; hence it is exceedingly difficult to determine what caused the improvement. I found, for instance, in my cases that in certain seasons the condition cleared up rather promptly, regardless of treatment. Of course, one of the criteria for a dermatophytid is that it should clear up more or less spontaneously. So I hope that the fraction that Drs. Peck and Glick have separated, which they call a skin test principle (Peck, S. M., and Glick, A.: Trichophytin: I. Methods of Preparation with Special Reference to the Specific Skin-Reactive Factor, ARCH. DERMAT. & SYPH. **43**:839 [May] 1941), may be the one to use for diagnostic purposes and that the other fraction may prove to be an immunizing one which will help. Of course, the latter must help in the focal infection, the primary infection itself; if it does not help in the primary infection, I see no value in these biologic methods.

The question of reinfection that the paper of Drs. Jamieson and McCrea has brought up brings to mind some cases that Dr. Williams and I followed for a number of years. Dr. Williams was most accurate in his work on fungous infections. When he examined a foot, he stated in the history the exact site at which he found the organism. I examined a number of these patients as late as six and seven years after the original diagnosis was made. Many of them were requested to return for a recheck; others came in because of other conditions. We were able to find the same organism that had been present originally in exactly the same site on the skin or nails, despite the fact that in many of the cases there had never been a relapse or any other clinical evidence of a fresh infection. That brings up the problem of reinfection from the standpoint of the shoe. I felt that most of the conditions that were presumably reinfections were simply exacerbations due to an organism that had always been present on the foot, probably in the same site, and for some reason had remained dormant.

Dr. Fred D. Weidman, Philadelphia: I am going to confine what I have to say to the matter of fractionation of the various antibodies, as brought up in the presentation by Drs. Peck, Glick and Weissbard. To begin with, the analysis of a fungous material (whether from cultures or tissues) into fractions is a matter of chemistry. In these materials there are multitudinous chemicals that must be regarded as possible adjuvants which will lead to the isolation of either the therapeutic or the desensitizing factor. The aim is to produce artificially a chemical condition which in test tubes is as close as possible to the natural chemical situation produced between the toes. That, of course, is the logical approach to specificity in the situation, by which avenue only can one expect to get increasingly specific reactions in tests on patients. Therefore, it is fundamental, when one tries to prepare or secure certain fungous chemicals for testing, that one use chemicals in the mediums which approach as closely as possible those on the feet or elsewhere. That is, if one uses a medium which has approximately the same nitrogen and carbohydrate content as the skin between the toes, approximately the same p_H, and so forth, there is a greater likelihood of securing specific substances in the test tube with which to work. That is a long preamble, but perhaps it may explain in part why Drs. Peck, Glick and Weissbard seem to have met with success with materials which were secured under a low p_H environment in the test tubes; the particular p_H with which they worked in the test tubes was of the same order as that between the toes.

After that, I think, the further work is that of fractionating. This is much more complicated than working with the bacterial antigens, because with these fungous plants, which have a much more complicated organization morphologically and physiologically, there is a much wider range of chemicals to be dealt with. But, at the same time, with that wider range, I think, there is a greater chance for securing more clearcut chemicals for fractions in which there are possibilities of identifying, or analyzing, ones that will be specific. One should not forget, perhaps, in thinking of ways and means of attacking further fractionation, the modern methods which are employed in the isolation of viruses, such as the ultracentrifuge.

A number of years ago I thought along these same lines when the Frei antigen was first discovered. Why is it that nobody has, as far as I know, attempted to fraction the Frei antigen?

Dr. Anthony C. Cipollaro, New York: I should like to comment on the paper by Drs. Greenwood and Rockwood. The method which they described has been found ineffectual at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, where iontophoresis has been used for

two or three years, not only with copper sulfate but with zinc sulfate, silver nitrate, saline solution and distilled water. In a few cases the condition seemed to improve, but it was my impression that the improvement was due to the fact that the patients were immersing their hands in a solution for half an hour every day. This method of treatment is messy, time consuming and expensive. The patients are required to take treatment daily or at least every other day.

I should like to say a word about the term iontophoresis. This is no criticism of the title of the paper, but the Council on Pharmacy and Chemistry and the Council on Physical Therapy of the American Medical Association prefer the use of the term common ion transfer to iontophoresis. According to the electrochemical experts, the term common ion transfer more accurately describes the process.

DR. F. J. EICHENLAUB, Washington, D. C.: It was not clear from what I heard of the paper by Drs. Miller, Stewart and Kimura whether they used a mixture of the three cultures that they obtained from each patient or whether they separated the patients culturally and used a specific antigen for the injections.

DR. ARTHUR M. GREENWOOD, Boston: In regard to Dr. Traub's comment, I think it involves a distinction in the functions of these various antiparasitic substances. These may function as protective agents when applied before inoculation. They act as disinfectants when applied after inoculation but before infection and as disinfestants if used to destroy a parasite after infection has taken place. The copper-containing floor covering mentioned by Dr. Traub might well act as a protective agent in the same way as many of the powders which are put into shoes. These powders would not be disinfectant but might be protective.

I was interested in the report, by Drs. Jamieson and McCrea, of 20 per cent microsporons found on glabrous skin or on the foot. I think this result shows that the fungous flora in their section of the country is different from that in New England. I do not know what Dr. Swartz's experience is, but I am sure Dr. Rockwood and I have found not more than 4 or 5 cases of microsporon infection of the glabrous skin in the last five years.

I think it is important not to draw too many conclusions from a series of cases of fungous infection, no matter how large it is in which dependence is based entirely on a clinical diagnosis.

DR. HIRAM E. MILLER, San Francisco: In answer to Dr. Eichenlaub, the preparations that my associates and I used were made from the three organisms mentioned. Each preparation was monovalent. For those who wish to use this product, it is put on the market by the Eli Lilly Company under the name undenatured fungous antigen.

DR. SAMUEL M. PECK, New York: I am the first to admit that the presentation by my associates and myself can be considered only as a preliminary report. As far as standardization is concerned, the Council on Pharmacy and Chemistry will not accept a standard until a great deal of work and chemical purification of these extracts is carried out. If our presentation is of any value, it indicates that the skin test principle and a desensitizing principle are not necessarily synonymous. Trichophytin at present is used both for testing and for treatment. As far as the skin test principle is concerned, I believe that my co-authors and I have demonstrated a practical method of preparation which takes very little time and is inexpensive. Although with our material, which is relatively free of skin test principle, we have been able to desensitize the majority of our patients, we have by no means proved that desensitization means clinical cure.

DR. ROBERT C. JAMIESON, Detroit: With Dr. Templeton's statement that cultures were more readily obtainable from damp materials I think Dr. McCrea and I are fully in accord. His remark about laundering of most of these materials, except the cotton socks which are subjected to higher temperature, I think is correct. If one were able to sterilize the socks thoroughly—and I think that can be done by ironing—one would be in a much better position to remove possible sources of reinfection. I believe, as others have stated, that in cases of reinfection the condition is probably not a true reinfection but a relapse or a flare-up of foci which had never entirely cleared up. In that respect, I am entirely in accord with Dr. Traub.

The limited experience I have had with the undenatured fungous antigen and with iontophoresis does not enable me to give an intelligent estimate of the possibilities, but I believe that the undenatured fungous antigen may be a potentially efficacious method of treatment and diagnosis in the future. As far as iontophoresis is concerned, with apologies to Dr. Cipollaro, I think this method is one which sometimes will be apparently effective and at other times ineffective. At least it will have one effect, which has not been mentioned, I think, in the treatment of these fungous infections, and that is a psychologic effect on the person treated.

INGESTION OF LARD IN THE TREATMENT OF ECZEMA AND ALLIED DERMATOSES

A CLINICAL AND BIOCHEMICAL STUDY

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Knowing of Hansen's results in the treatment of infantile eczema from the feeding of unsaturated fatty acids, as well as those of Cornbleet, Ginsberg and others, and having learned that Burr found lard a particularly rich source of unsaturated fatty acids, a little over two years ago one of us (C. W. F.) prescribed lard to be taken by mouth to a group of 42 ambulatory patients who were suffering from various forms of chronic dermatitis. They were of all ages, from infancy to well past middle age. Thirty-one of these were followed for variable periods, and the majority of them were thought to have shown some degree of improvement after having taken lard for from a few weeks to a few months. These patients were not well controlled, but the results appeared encouraging enough to warrant further and better controlled study. The results obtained in these original cases are not incorporated in this paper because of the fact that they received insufficient study. They merely served to lend the impression that the internal administration of lard apparently rather frequently relieved the itching to some degree and thereby allowed the skin a better chance to heal.

Like most observers, we believe that sensitization factors are chiefly responsible for the so-called eczemas. We have reason to believe, however, that in many of the persons so afflicted there are certain deficiency factors about which relatively little is known at present.

As a result of the comparatively recent findings with regard to the essential nature of fats in the diet of animals, the value of fat in the

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This work was aided by a grant from the National Live Stock and Meat Board.

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Read at the Sixty-Fourth Annual Meeting of the American Dermatological Association, Inc., New Orleans, April 7, 1941.

normal diet of man has received considerable investigation. In 1929 Burr and Burr [1] first showed that a definite deficiency disease was produced in rats when the animals were fed diets lacking in fat. Among the cutaneous manifestations of the disease were a pronounced erythematous, scaling dermatitis, said to be somewhat analogous to eczema in man; localized swellings, somewhat similar to those of angioneurotic edema; abundant dandruff-like scaling, similar to that in seborrheic dermatitis, and alopecia, such as may accompany or follow seborrheic dermatitis. The animals also showed various systemic, endocrine and visceral disturbances, such as inanition, inhibited growth, anorexia, renal lesions and impairment of mating instinct. The condition was cured by the addition of certain unsaturated fatty acids to the diet.[2] Linoleic acid, particularly, and arachidonic acid, a highly unsaturated fatty acid of animal origin, were found to possess the necessary curative properties. Linolenic acid, which is so abundant in linseed oil, and the highly unsaturated acids of cod liver oil were found to cause renewed growth of the animals but did not eradicate the condition of the skin.

This work was confirmed by Evans and Lepkovsky.[3] The work of these two groups of authors was confined to experiments with small animals. Hansen,[4] however, in 1933, reported that he had fed oils rich in unsaturated fatty acids to a number of eczematous children, bringing about an improvement in the cutaneous disease and an elevation of the iodine number of the serum lipids to essentially normal. Cornbleet and Pace [5] in a clinical study obtained gratifying results from the use of refined maize oil in 87 patients with eczema. They stressed the importance of administering the oil in sufficient quantities and over a prolonged period, the average time required for obtaining satisfactory results being from twelve to eighteen months. Ginsberg, Bernstein and Iob,[6] using chiefly raw linseed oil in adults and corn oil in infants, concluded that the patients so treated got along no better than those who received no such treatment or any other treatment. They found no great difference between the blood values for patients with neurodermatitis or infantile eczema and those for normal subjects. Faber and Roberts,[7]

1. Burr, G. O., and Burr, M. M.: J. Biol. Chem. **82**:345, 1929.

2. Burr, G. O., and Burr, M. M.: J. Biol. Chem. **86**:587, 1930. Burr, G. O.; Burr, M. M., and Miller, E. S.: ibid. **97**:1, 1932.

3. Evans, H. M., and Lepkovsky, S.: J. Biol. Chem. **96**:143, 1932.

4. Hansen, A. E.: Proc. Soc. Exper. Biol. & Med. **31**:160, 1933.

5. Cornbleet, T., and Pace, E. R.: Use of Maize Oil (Unsaturated Fatty Acids) in the Treatment of Eczema, Arch. Dermat. & Syph. **31**:224 (Feb.) 1935.

6. Ginsberg, J. E.; Bernstein, C., Jr., and Iob, L. V.: Effect of Oils Containing Unsaturated Fatty Acids on Patients with Dermatitis, Arch. Dermat. & Syph. **36**:1033 (Nov.) 1937.

7. Faber, H. K., and Roberts, D. B.: J. Pediat. **6**:490, 1935.

on the other hand, reported a slightly lower than normal iodine number in infants with eczema but considered the findings secondary rather than etiologic. Taub and Zakon [8] in a small series of cases of atopic dermatitis observed that some patients actually became worse on taking raw linseed oil internally.

The relation between the unsaturated fatty acids and vitamin B_6 (pyridoxine) is as yet not clearly defined, in spite of the painstaking experiments of a number of investigators. Gross [9] stressed the importance of the unsaturated fatty acids, especially linoleic acid, for the proper functioning of vitamin B_6 in the rat. Schneider, Steenbock and Platz [10] showed that the so-called acrodynia of the rat can be cured by the essential fatty acids independent of vitamin B_6, or it can be cured by the rice-bran concentrate independent of fatty acids. Salmon [11] stated the belief that vitamin B_6 and the essential fatty acids can within limits mutually alleviate the deficiency of each other.

In the animal experiments conducted by Burr and Burr, fresh lard, which they among others showed to be a rich source of the two particularly important unsaturated fatty acids, linoleic and arachidonic, was found to be one of the best curative fats. In the study reported in this paper, therefore, lard was employed as a dietary source of these essential fatty acids. It was chosen also because of the fact that it is an easily digested fat that is extensively used in cookery. Various authors who used the vegetable oils repeatedly stressed the fact that corn oil, and particularly linseed oil, commonly caused gastrointestinal disturbance. Although animals are able to synthesize saturated fatty acids, such as stearic acid, there is evidence in the literature to indicate that they are unable to synthesize highly unsaturated fatty acids, particularly linoleic acid, and hence must derive their necessary supply from dietary fats. However, in order to supply the so-called "essential fatty acids," it is not sufficient merely to feed a fat or oil with a high iodine number, indicating a high degree of unsaturation of the fatty acids; the fat or oil must contain the essential fatty acids, linoleic and arachidonic. The lard used in this study was high grade, fresh, steam-rendered lard prepared from 100 per cent cutting fats, thus assuring minimum oxidation of the unsaturated fatty acids linoleic and arachidonic.

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8. Taub, S. J., and Zakon, S. J.: The Use of Unsaturated Fatty Acids in the Treatment of Eczema, J. A. M. A. **105**:1675 (Nov. 23) 1935.

9. Gross, P.: J. Invest. Dermat. **3**:505, 1940.

10. Schneider, H.; Steenbock, H., and Platz, B. R.: J. Biol. Chem. **132**:539, 1940.

11. Salmon, W. W.: J. Biol. Chem. **133**:lxxxiii, 1940.

GENERAL CONSIDERATIONS

In the present study care was taken not to include patients who had recently had fever, who had lost or gained an excessive amount of weight or who had recently been subjected to rigid dietary restrictions or to unusual medication, for the iodine number of blood fats is known to be affected by such factors as age, infection, character of the diet, prolonged starvation, excessive muscular exercise, anemia and other pathologic conditions and degree of activity of certain endocrine factors.

Considerable difficulty was encountered in appraising the results of treatment, as would be expected, in that the results could not be accurately measured, especially in a group of diseases such as the eczemas, in which many influences other than the treatment often are responsible for improvement, there being a characteristic tendency in these diseases to spontaneous remissions and recurrences. Brunsting [12] has recently stressed the influence of such factors as climate, weather, dietary indiscretions, exposure to irritating dusts, intercurrent infections, physical and emotional stress and fatigue, all of which at irregular intervals influence the condition of the skin in the eczema syndrome, which is so commonly accompanied by asthma and hay fever. Statements made in this paper with regard to benefit from treatment have, therefore, been determined as cautiously as possible. It can simply be stated that while taking lard a given patient either did or did not show improvement, regardless of what factors may have been responsible for any noted improvement. It was borne in mind that on hospitalization of an eczematous patient the eruption usually improves as the result of an abundance of rest and relative freedom from exposure to irritants. We therefore have stated not that lard caused any noted improvement but only that such improvement occurred—when it did occur—while these patients were taking lard.

We appreciate the personal equation in evaluating the degree of improvement of an eruption, for commonly two physicians do not estimate it the same, to say little of the fact that the patient's opinion of it may be different from the physician's.

The word improvement is here used to indicate subjectively a decrease in itching and objectively a more normal appearance of the skin, temporary though it may be. By general improvement of the patient we indicate that he has stated that he is sleeping better and feels stronger and better in general.

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12. Brunsting, L. A.: Atopic Dermatitis (Disseminated Neurodermatitis) of Young Adults, Arch. Dermat. & Syph. **34**:935 (Dec.) 1936.

For all of the patients studied, the ambulatory and the hospitalized ones alike, as little local treatment as possible was employed, although in many instances some locally applied medicament had to be used, such as a calamine lotion or a simple protective paste, by way of satisfying the patient and temporarily relieving him to some extent of his discomfort. To satisfy some of the ambulatory patients even roentgen therapy in a dose of ⅛ or ¼ skin unit (37 to 75 r) was administered to one or more areas.

It should be mentioned that 6 of 107 eczematous patients could not have their results included in this report, 2 because of gastrointestinal disturbance, 2 for psychic reasons (the thought of taking lard) and 2 because treatment was stopped because of gain in weight.

TABLE 1.—*Ambulatory Patients Who Took Lard from One to Seven Months (No Study of Blood)*

Diagnosis	Number of Patients	History of Other Allergies	Patients Who Used Placebo or Other Local Treatment		Patients Given No Other Therapy		Total Number Considered Improved by Patient and by Physician
			Number	Number Improved	Number	Number Improved	
Atopic dermatitis (generalized)	36	16	24	17	12	5	22
Chronic contact dermatitis (hands and forearms chiefly)....	10	2	4	2	6	2	4
Seborrheic dermatitis (extensive).....	8	2	5	3	3	2	5
Infectious eczematoid dermatitis (upper extremities chiefly)...	6	2	4	2	2	0	2
Totals.....	60	22	37	24 (65%)	23	9 (39%)	33 (55%)

CASES STUDIED

Of the 60 ambulatory patients who took lard but had no studies of the blood and who therefore were studied clinically only, 36 suffered from generalized atopic dermatitis; 10 from chronic contact dermatitis, which involved chiefly the hands and forearms; 8 from seborrheic dermatitis, which involved chiefly the face, ears, scalp and folds of the body (fungous disease was excluded), and 6 from so-called infectious eczematoid dermatitis, involving chiefly the upper extremities. These patients were observed for from four months to over a year and took lard steadily for periods of four weeks to seven and one-half months (table 1).

All of the 18 hospitalized patients were suffering from atopic dermatitis, the so-called generalized neurodermatitis. All of the 29 ambulatory patients for whom studies of the blood were performed were similarly affected.

METHODS OF STUDY

Eighteen patients in whom changes in the composition of the blood fat were observed were hospitalized for two to seven weeks. They were given a normal quantitative diet during this period. The normal diet was considered complete with respect to all dietary requirements, including adequate amounts of vitamin B_6, the vitamins being supplied in the form of meat, milk, fresh fruits and vegetables. The quantitative diet permitted 1.25 to 1.5 Gm. of protein and 2 Gm. of fat per kilogram of body weight and sufficient carbohydrate to allow 35 calories per kilogram of body weight per day. The dietary fat consisted of 10 Gm. of bacon and the rest in the form of butter and olive oil. (In the experiments with small animals neither butter nor olive oil had been found to be effective as curative fats for the scaliness resulting from a fat deficiency.)

In order to follow any changes in composition of the blood fats of the patients, an initial fasting blood determination was made when each patient was admitted to the hospital. A second determination was made after one week of the normal diet alone and subsequent determinations at one to two week intervals thereafter. Three tablespoons of lard was given daily in addition to the normal diet after the first week.

Since it is believed that the beneficial effects of lard lie in its fatty acid fraction, the chemical analyses of the blood serum were confined to a quantitative determination of the total fatty acid content, the iodine number and the polybromide number of the fatty acid fraction.

The iodine number of the fatty acids derived from serum lipids may be used as an indication of the degree of unsaturation of the total fatty acid fraction, which includes all the unsaturated fatty acid in the serum. There is no satisfactory direct method for the quantitative determination in the blood of linoleic acid alone.

The polybromide number, on the other hand, is a measure of the amount of fatty acid containing four or more double bonds. The principal animal fatty acid of this type is arachidonic acid. The polybromide number, therefore, may be used as an index of the relative amount of arachidonic acid in the blood.

For these analyses, the microgravimetric technic of Wilson and Hansen [13] was used for determining the total fatty acids, the Yasuda [14] microreagent was used for determining the iodine number of the fatty acids, and the polybromide numbers were determined by bromination of the purified fatty acids in ethyl ether at 0 C.

For the sake of comparison and interpretation of the results, similar chemical determinations were made of the serums from 10 normal adults.

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13. Wilson, W. R., and Hansen, H. E.: J. Biol. Chem. **112**:457, 1936.
14. Yasuda, M.: J. Biol. Chem. **94**:401, 1931.

These results are given in table 2. The average value for the iodine number of the fatty acids in this group is somewhat lower than the average values reported by some authors.

Some of the results of the chemical study of the blood serums of the hospitalized patients, together with clinical observations, are given in tables 3 and 4.

COMMENT

No significance is attached to the values for total fatty acids in tables 3 and 4 except to show that the values for eczematous patients fall in the normal range and that feeding 3 tablespoons of lard does not increase the total fatty acid content of the blood above normal. It will also be observed that the polybromide number of the fatty acid for

TABLE 2.—*Determinations of Fatty Acids in the Fasting Blood Serums of Normal Adults*

Subject	Total Fatty Acids,* Mg. per 100 Cc. of Blood	Iodine Number	Polybromide Number
1	331	103.9	13.0
2	438	98.5	7.7
3	312	101.5	10.2
4	277	100.3	7.0 †
5	217	101.5	7.8
6	498	95.1 ‡	7.3
7	324	99.8	...
8	295	96.2	8.0
9	319	95.7	7.7
10	325	98.7	7.7

* Total fatty acids vary from 217 to 498.
† Lowest polybromide number.
‡ Lowest iodine number.

all hospital patients was normal when the patients were admitted. With the ingestion of lard, the polybromide values sometimes increased before a change in the iodine number was noted, but there was no corresponding change at this time in the clinical condition of the patient. This would seem to indicate that eczematous patients are not deficient in arachidonic acid. The polybromide determinations were discontinued after ninety determinations had been made and no correlation observed with the clinical condition.

It will also be noted from tables 2, 3 and 4 that the lowest iodine number of the fatty acids found for the group of normal adults was 95 and that the iodine numbers of 9 of the 18 hospitalized patients, or 50 per cent, fell below this minimum value. All of the patients with iodine numbers below 95 showed decided clinical improvement in about three weeks with a corresponding rise in the iodine number after lard was included in the diet. Of these results only the values for the serum on the day the patient left the hospital are given, but a change in the

TABLE 3.—*Chemical Studies of the Blood and Clinical Observations on Hospitalized Patients with Atopic Eczema*

Patient	Age	Sex	Duration of Eczema	Symptoms on Admission	Serum Fatty Acids									Hospital Days	Condition After Taking Lard in Hospital
					On Admission			After Normal Diet			Day of Discharge				
					Total Fatty Acids*	Iodine Number	Polybromide Number	Total Fatty Acids*	Iodine Number	Polybromide Number	Total Fatty Acids*	Iodine Number	Polybromide Number		
1	29	♂	Age 2-4, 21-29	Scaling, crusting and much infiltration of face and extremities	280	101.8	8.7	306	99.4	7.8	281	96.8	8.4	34	No improvement
2	22	♀	Age 10-22	Scaling dermatitis and weeping only on ears and scalp and in cubital regions; much infiltration	289	88.5	6.6	368	87.8	8.5	331	93.4	10.2	47	Great improvement in all areas
3	22	♀	Entire life	Scaling dermatitis and moderate infiltration on head, neck and chest chiefly	290	92.4	6.9	233	85.6	9.5	215	101.9	...	49	"Best in entire life; skin thinner, smoother; itching gone"
4	35	♂	3 years; intermittent age 26-35	Scaling crusting dermatitis, general distribution; much infiltration	467	89.9	7.8	308	99.2	8.6	302	98.9	8.6	14	Moderate improvement; "skin bleached and flexible"
5	9	♂	Entire life	Scaling crusting dermatitis, general distribution; much infiltration	308	90.0	9.4	314	87.9	8.9	307	103.0	9.5	31	Much improvement; trunk normal; "skin soft and pliable"
6	9	♀	Entire life	Cubital regions and neck; exudative; dry; thighs and upper part of chest; dry; moderate infiltration	305	101.2	...	317	98.7	8.2	344	108.9	12.4	30	Much improvement; almost entirely clear
7	19	♀	Entire life	Much infiltration; scaling dermatitis chiefly on neck, chest, scalp and in cubital regions	254	98.4	13.0	287	99.7	11.6	255	106.2	10.0	30	Slight improvement; "skin softer, less itching"
8	25	♂	Age 17-25	Scaling, crusting dermatitis, chiefly on face and neck	320	90.6	7.6	242	85.6	6.5	257	98.0	10.4	43	Moderate improvement; "best in four years"

9	81	♀	1 year	Scaling fissured dermatitis, chiefly on extremities	388	97.5	8.6	398	98.4	9.2	451	100.4	8.6	43	Moderate improvement
10	29	♂	25 years	Scaling and crusting on head, neck and upper extremities	...	.....	...	324	93.7	8.6	371	95.5	7.9	16	Slight to moderate general improvement
11	17	♀	Entire life	Scaling dermatitis and moderate infiltration on flexor surface of arms and forearms chiefly	305	91.2	9.1	261	95.2	11.1	257	95.0	11.0	19	Nearly clear
12	18	♂	Infancy, also age 11-18	Scaling dermatitis and much infiltration of face, neck and cubital regions; eyebrows absent	311	89.9	8.9	307	97.0	10.3	300	101.5	...	46	Much improvement; face entirely clear; eyebrows regrown
13	23	♂	Since infancy	Mild dermatitis of the face and cubital regions; in remission; history of frequent and severe exacerbations	256	99.7	...	298	100.6	...	280	94.4	...	13	Continued improvement (father, a physician, states patient never was so well)
14	18	♀	Entire life	Much infiltration on face and neck and in cubital regions chiefly	...	....	...	425	100.7	...	371	109.1	...	30	Much improvement
15	13	♂	Entire life	Scaling and excoriation; general distribuation	439	93.6	...	383	101.3	...	333	107.5	...	32	Great improvement
16	28	♀	Entire life	Generally distributed scaling crusting dermatitis and moderate infiltration	304	98.2	...	300	101.8	...	315	101.1	...	40	Much improvement
17	23	♀	Entire life	Much scaling crusting dermatitis chiefly on face and neck and in cubital and popliteal regions	284	99.2	...	292	98.8	...	296	100.2	...	29	Moderate improvement
18	15	♂	Entire life	Scaling and crusting on face and in cubital regions chiefly	291	104.7	...	289	104.6	...	287	103.7	...	29	Considerably better

* Expressed in milligrams per hundred cubic centimeters.

clinical condition, for instance when itching ceased or weeping stopped, was almost always reflected in a rise in the iodine number. From five to twenty specimens of blood were taken from each patient in the hospitalized group. The clinical changes observed with the ingestion of lard were not so striking in the other 50 per cent of the patients, i. e., those who did not have low iodine numbers when admitted to the hospital. With a single exception there was a general improvement in the eruption, but only one third of these patients showed decided improvement. It was not possible to keep the patients in the hospital indefinitely to see if complete clearing of the skin could be accomplished under the

TABLE 4.—*Summary of Chemical Studies of the Blood of Hospitalized Patients with Atopic Eczema*

		Average Values for Serum Fatty Acids									
		On Admission			After Normal Diet			Day of Discharge			
Patients	Number	Total Fatty Acids*	Iodine Number	Polybromide Number	Total Fatty Acids*	Iodine Number	Polybromide Number	Total Fatty Acids*	Iodine Number	Polybromide Number	Condition on Day of Discharge
With subnormal iodine numbers (below 95)	9	341	90.7	8.0	304	92.6	9.0	297	99.4	9.6	1 with slight improvement; 8 with great improvement
With normal iodine numbers (above 95)	9	296	100.0	10.1	323	100.3	9.2	320	102.3	9.8	1, no change; 5 showed slight general improvement and 3 great improvement
Average.....		318	95.3	9.0	313	96.4	9.1	308	100.8	9.7	Summary: 1, no change; 6 showed slight general improvement and 11 great improvement

* Expressed in milligrams per hundred cubic centimeters.

hospital conditions. However, the patients reported for observation and chemical analysis of the blood at intervals of two weeks to one month. One patient's skin cleared entirely after she left the hospital and has remained clear to the time of writing, a period of six to eight months; her eruption had been present all of her life. In some instances the condition of the skin became worse the first week after the patient left the hospital, and in these the iodine number of the fatty acids usually showed a corresponding decrease in value. However, too much emphasis should not be placed on one iodine value. There is a variation in iodine values even for normal adults, as will be shown in table 5, but none of the values for the normal persons falls below the minimum of 95.

Chemical studies were also made of the serums of 29 ambulatory patients, 48 per cent of whom had low iodine numbers, which may indicate a deficiency of unsaturated fatty acid. In cases of eczema in which clinical improvement and a rise in the iodine number resulted from the addition of lard to the diet, there was a strong suggestion that the low iodine number was due to an actual deficiency of unsaturated fatty acids rather than to faulty fat metabolism.

STUDIES OF NORMAL BLOOD

Since it is commonly observed that eczematous conditions become worse during the cold months of the year and that dryness and itching of the skin are particularly common among normal persons during this period, it seemed desirable to ascertain, if possible, whether the require-

TABLE 5.—*Variations in Serum Fatty Acids of Normal Adults* *

Date	Patient C. W. F.		Patient R. B. C.		Patient E. C. O.		Patient E. D. P.		Patient H. F. W.	
	Total Fatty Acids	Iodine Number	Total Fatty Acids	Iodine Number	Total Fatty Acids	Iodine Number	Total Fatty Acids	Iodine Number	Total Fatty Acids	Iodine Number
9/19/40	332	106.2	301	104.0	371	105.0	323	103.1	313	104.9
10/ 2/40	...	.....	302	108.3	371	106.8	312	105.6	299	108.0
10/ 9/40	349	111.2	260†	110.8	400	104.1	356	105.8	320	107.3
10/23/40	282	114.5	308	109.1	354	106.5	362	100.7	282	111.1
10/30/40	400	106.4	325	102.4	398	100.9	371	97.0‡	311	107.6
11/13/40	343	110.1	324	107.8	364	108.3	357	105.6	320	110.6
12/31/40	332	105.7	291	103.6	347	106.7	356	104.3	304	110.2
1/31/41	337	111.3	279	106.5	409	104.6	375	106.8	286	109.3
3/19/41	321	112.4	294	107.8	382	108.7	363	109.1	355	110.1

* It is apparent that even in the colder months the total fatty acids and the iodine numbers in noneczematous persons do not fall below the minimum observed in table 2.
† Lowest value for total fatty acids.
‡ Lowest iodine number.

ment for unsaturated fatty acids was greater at this time. If noneczematous, or so-called normal, persons did not ingest more fat containing unsaturated fatty acids during this period, it appeared possible that the unsaturated fatty acid fraction of the blood fat of these persons might be less during the time that the skin was dry and pruritic. This could be detected by a drop below the normal range in the iodine number of the fatty acids.

For this purpose the total fatty acid content and the iodine number of the fatty acid fraction of the blood serums of 5 normal persons were determined at frequent intervals during the fall months (Sept. 19 to Nov. 13, 1940) and at four to six week intervals during the following four months (Nov. 13, 1940 to March 19, 1941). The results of these studies are given in table 5.

It will be noted that, although there is a fluctuation in the iodine number of the fatty acids for each person during the six months, none

of the values fall below the normal range previously observed (table 2) and they are all well above the values for the fatty acids in many cases of eczema.

Factors other than seasonal conditions, therefore, must be responsible for the low iodine numbers observed for the fatty acids of the serums of eczematous persons.

SUMMARY AND CONCLUSIONS

In the group of 18 hospitalized patients, 9 (50 per cent) had subnormal iodine numbers of the fatty acids when admitted to the hospital. The decided improvement in the clinical condition in these patients was coincident with a rise in the iodine number of the serum fatty acids after lard was added to the diet. Of the remaining 50 per cent of the hospitalized patients, in whom the fatty acids of the blood serums yielded normal iodine values when the patients were admitted to the hospital, one third showed decided clinical improvement, 1 showed no appreciable change and the remainder showed slight or general improvement when lard was added to the diet. The skin of but 1 patient cleared entirely. No patient was considered cured.

Although the polybromide value of the fatty acids, taken as a measure of the arachidonic acid content, often increased when lard was added to the diet of a hospitalized patient, there was no corresponding change in the clinical condition, which would indicate that eczematous patients are not deficient in arachidonic acid.

In this study the ingestion of lard has been found to have some beneficial effects in relieving eczematous patients. After treatment for a variable number of weeks, in about half the patients the itching became less pronounced, which in itself accounted for less scratching, thereby allowing the skin to become less inflamed, as evidenced by less redness, less thickening and less scaling and crusting. Exacerbations were more common in those who had stopped taking lard than in those who had not. A number of the hospitalized patients had recurrences soon after leaving the hospital even though they were continuing to take lard, undoubtedly the result of nervous, dietary and contact factors. Usually a decrease in the iodine number accompanied such an exacerbation, this number subsequently rising as improvement occurred. Among common remarks made by the patients in the improved group were that they slept better and felt stronger.

In patients with eczematous eruptions the composition of the blood may or may not fall within the range of normal values found in noneczematous persons. The blood serums of 49 per cent of the 47 eczematous patients for whom blood studies were made yielded low values for the iodine number of the fatty acids. It was this group that showed the most clinical improvement when lard was added to the diet.

Ingestion of lard over a period of several weeks increased the iodine number of the fatty acids in this "deficient" group, sometimes up to the normal degree of unsaturation of the blood fat. Clinical improvement occurred simultaneously with the rise in the iodine values. This was particularly evident in the group of hospitalized patients, all of whom, with 1 exception, showed decided improvement.

Since normal variations in the iodine number of the fatty acids, even during the cold months of the year, are well above the low values observed in 49 per cent of the eczematous patients, factors other than seasonal conditions must be considered responsible for these low values.

ABSTRACT OF DISCUSSION

DR. RICHARD L. SUTTON JR., Kansas City, Mo.: Brown and collaborators (Brown, W. R.; Hansen, A. E.; Burr, G. O., and McQuarrie, I.: Effects of Prolonged Use of Extremely Low-Fat Diet on an Adult Human Subject, *J. Nutrition* **16**:511-524 [Dec.] 1938) gave a human volunteer a practically fat-free diet, providing him with vitamin A but with a smaller fat intake than Burr and Burr gave to their rats. The man stayed on the diet for about sixty days and suffered no ill effect. It relieved his migraine, in fact. While it is generally accepted that unsaturated fatty acids are necessary for the welfare of the rat, it does not follow that they are necessarily essential for human beings. I do not know how pertinent that is to the authors' study, for I am a great believer in the empiric. I believe that if something works, its explanation can be figured out afterward.

DR. M. H. EBERT, Chicago: Like the last speaker, I am a thorough believer in the empiric, and I am impressed by the results which were obtained in the 18 hospitalized patients.

I think this was a good experiment because such factors as hospitalization and separation from home irritants, both outside irritants and inhalants and psychogenic factors, were the same for the two groups. I realize the series is small, but the amount of chemical work involved was enormous.

DR. CLARK W. FINNERUD, Chicago: It has only been in recent years that considerable interest has been aroused in this problem of the needs of the various unsaturated fatty acids in the diet of animals and of human beings. This paper is not a plea for anything but merely a report of a biochemical study of the blood fats in patients with eczema and related diseases and an attempt to evaluate any benefits to be derived by such patients from the unsaturated fatty acids in lard.

ABSORPTION OF EXTERNALLY APPLIED AMMONIATED MERCURY

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Scattered through the literature are a number of records of damage associated with the use of various ointments containing insoluble compounds of mercury. It is a common belief that such use may be associated not only with varying degrees of local irritation but also with general effects varying from slight functional disturbance to fatal damage. Indeed, merely because such materials contain the potentially dangerous mercury, little hesitation is manifested in accepting such views without further question.

Today the problem has assumed a new and practical aspect for two reasons. The first is that the new food and drug laws have given the authorities the power to remove dangerous materials from public availability; the second, that new physiologic and pathologic conceptions of repair processes raise the interesting question whether small, individually innocuous doses of this type of material can really lead to poisoning.

The use of mercury on the skin by both the physician and the laity is exceedingly great. A conservative estimate of its annual use in this country amounts to over a million packages of some form of ammoniated mercury ointment, in addition to that prescribed by members of the medical profession, and other forms of mercury, such as red mercuric oxide or the lotions of mercuric chloride. In spite of this extensive use and in spite of the many writings concerning the beneficial and the harmful results of this material, we have been unable to find a single serious study checked by accurate analyses on ammoniated mercury.

These studies were made possible by a grant from the External Products Research Institute.

From the Pharmacology Department of the University of Tennessee, Memphis, Tenn., and the Pathology Department of Columbia Hospital, Milwaukee.

Several studies have been made on somewhat similar compounds, such as mild mercurous chloride, and these have been especially enriched by the careful experiments of Sollmann and his colleagues,[1] whose work is almost unique in that a sufficiently accurate method of analysis was adopted.[2] Nevertheless, to argue about the likelihood of analogous results being obtained in a matter which is essentially a quantitative problem, and thus subject to many obscure variations, is dangerously unscientific and practically unsound.

We have therefore conducted a large series of experiments on animals and man, in order to define more clearly the real or fancied dangers of the practical use of ammoniated mercury. The experiments we wish to report concern solely the effect of this material as applied to the human skin, the larger part of our work on animals being destined for a more appropriate technical journal. While the skin of animals differs considerably from that of man, being in the species used entirely devoid of sweat glands and bearing considerable fur, it may be of interest to record in passing that over twenty thousand local applications made daily to the shaved (with fine electric clippers) skin of cats, dogs, rabbits and rats (108 animals) for continuous periods of from three to twelve months never produced local irritation as observed either on inspection or on microscopic examination (G. H. H.). The animal work included the use of 2, 5 and 10 per cent ammoniated mercury and 5 and 10 per cent red mercuric oxide in a simple petrolatum base.

We may conclude without hesitation that these ointments are not irritating to the skin of such animals. Rashes which occur on the human skin are therefore to be associated more with the peculiarities of this structure than with the irritant properties of the compounds used. This view is supported by the fact that unquestioned irritants, such as sulfides, affect the skin of these animals as violently as that of man, a

1. (*a*) Cole, H. N., and Sollmann, T.: Clinical Excretion of Mercury, Arch. Dermat. & Syph. **17**:625 (May) 1928. (*b*) Cole, H. N.; Gammel, J. A.; Schreiber, N. E., and Sollmann, T.: Mercuric Salicylate: Study of Its Excretion in Treatment of Syphilis, ibid. **19**:105 (Jan.) 1929. (*c*) Cole, H. N.; Rauschkolb, J. E.; Schreiber, N. E., and Sollmann, T.: Massive Weekly Inunctions with Mercury, ibid. **20**:176 (Aug.) 1929. (*d*) Cole, H. N.; Schreiber, N. E., and Sollmann, T.: Mercurial Ointments in the Treatment of Syphilis, ibid. **21**:372 (March) 1930. (*e*) Sollmann, T.; Cole, H. N.; Schreiber, N. E.; De Wolf, H. F., and Van Cleve, J. V.: Mercurial Inunctions in the Treatment of Syphilis, ibid. **27**:1 (Jan.) 1933.

2. (*a*) Sollmann, T.; Cole, H. N.; Schreiber, N. E.; De Wolf, H. F., and Van Cleve, J. V.: Mercury Inunctions, Arch. Dermat. & Syph. **32**:242 (Aug.) 1935. (*b*) Booth, H. S., and Schreiber, N. E.: J. Am. Chem. Soc. **47**:2625, 1925; **48**: 1815, 1926. (*c*) Schreiber, N. E.; Sollmann, T., and Booth, H. S.: ibid. **50**:1620, 1928.

fact well known to those who have tried to use depilatory substances on animals.

It is known that all insoluble preparations are as such inactive. Ammoniated mercury must be in solution before it can exert a pharmacologic action. Moreover, all heavy metals readily form complexes with protein and in so doing may liberate, more or less completely, any associated acid. The corrosion of mercury bichloride is thus due not to the mercury but to the liberated hydrochloric acid; the corrosion of toughened silver nitrate is due to the liberated nitric acid and not to the silver. The use of such metallic salts in places where acid of sufficiently high concentration may be liberated is thus likely to produce some irritation, which is, however, due to an acid and not to a specific metal. The chlorides and nitrates of many common metals are particularly irritating. Insoluble salts must be rendered soluble before they exert any action, and since this process is usually slow, they do not commonly produce this local irritation.

METHOD AND MATERIAL

The quantitative analysis of small amounts of mercury involves considerable technical difficulties, especially when present in organic material. We have used the method of Stock,[3] which is basically similar to that used by Sollmann and his co-workers. For this purpose, we developed a plant capable of carrying out about twenty estimations per day [4] (which was possible by the use of a staggered method) for the entire analysis, carried on for five days. We were able to recover about 70 per cent of mercury from the tissues, in the order in which we were interested, namely, from 0.1 to 3,000 micrograms of mercury per hundred grams (or centimeter) of material. The method ends with the direct measurement of a globule of metallic mercury and, apart from technical losses, is thus positive in meaning. Having conducted over two thousand such analyses, we are in a position to state, as our modest predecessors failed to record, that the use of this method is beyond the powers of any but the most competent chemical technician and therefore is not suitable for routine clinical work.

All the following experiments were conducted on presumably healthy male medical students. The ointments used in these studies were specially prepared as a research formula by Parke, Davis & Co., Detroit.

After collecting a preliminary total of one twenty-four hour specimen of urine and feces, the subject was taught how to apply 1 Gm. of ointment to the flexor surface of his left forearm. This was done with a flat steel spatula. The ointment was smeared on well but without undue rubbing. This amount left the area of skin somewhat greasy. The application was made in the laboratory daily, except

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3. Stock, A.; Lux, H.; Cucuel, F., and Gerstner, F.: Ztschr. f. angew. Chem. **44**:200, 1931. Stock, A.; Lux, H.; Cucuel, F., and Köhle, H.: ibid. **46**:62, 1933. Stock, A.; Cucuel, F., and Köhle, H.: ibid. **46**:187, 1933. Stock, A., and Cucuel, F.: ibid. **47**:641, 1934. Stock, A., and Neuenschwander-Lemmer, N.: Ber. d. deutsch. chem. Gesellsch. **71**:550, 1938.

4. Report of Studies from External Research Institute (National Toilet Company, Paris, Tenn.), vol. 1, privately issued, September 1940.

Sundays, for four weeks. Twice a week specimens of twenty-four hour collections of urine and feces, kept in carefully cleaned jars, were analyzed. The week following the discontinuation of application of the ointment a specimen was also studied, making ten in all.

RESULTS

The initial analyses of the excreta of our subjects, recorded in tables 1 and 2, showed that the average total excretion in terms of metallic mercury was 17.6 micrograms per day. This, allowing for the known analytic losses, suggests a daily intake and output, or body stream, to be in the order of 20 micrograms. The urine contains somewhat less than half of this total, 7 to 8 micrograms. Cases 8 and 12 showed an unusually high fecal content, not reflected in the urine. As these figures were not repeated they almost certainly represent an accidental oral ingestion of some insoluble compound. They do illustrate, however, the fact, commonly encountered both in animals and in man, that undiscovered sources of ingestion exist. These figures are not included in the average.

Analysis of foods, the details to be published elsewhere, shows that they practically all contain mercury, varying in amounts from a trace to 5 to 6 micrograms per hundred grams. Fresh vegetables and eggs and one specimen of crackers contained no mercury. From this and other data we conclude that since all persons are continually ingesting a small quantity of the element in their food and also continually excreting it in the urine and feces, the presence of small amounts in both food or excretions has no toxicologic significance. Moreover, Stock,[5] Bodnár, Odon and Weszprémy [6] and we have found mercury always present in all human tissues examined. Moreover we add to the list the tissues of dog, cat, rabbit, rat, frog, cow, hog and fish, including newborn offspring of both animals and human beings and also fetuses of animals. Bodnár, Odon and Weszprémy [7] even suggested a biologic role for mercury.

In table 1 are given the results obtained from the daily application of 1 Gm. of a 10 per cent ammoniated mercury ointment. From them may be calculated that the application of 24 Gm. of ointment, containing 2.4 Gm. of ammoniated mercury, increased the entire mercury excretion for the month by 0.5 mg. This amounts to 1 part in 3,800 parts actually applied. By comparison, 1 grain (0.06 Gm.) of mild mercurous chloride taken by mouth would take a hundred months at this rate of excretion.

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5. Stock, A.: Biochem. Ztschr. **304**:73, 1940.

6. Bdonár, J.; Odon, S., and Weszprémy, B.: Biochem. Ztschr. **302**:384, 1939.

7. Bodnár, Odon and Weszprémy,[6] p. 389.

TABLE 1.—*Excretion of Metallic Mercury in the Urine and Feces of Human Beings After the Daily Application of One Gram of Ten Per Cent Ammoniated Mercury Ointment*

	Urine, Micrograms of Mercury					Feces, Micrograms of Mercury					Total Daily Average
Case	Initial	Minimum	Maximum	Final	Daily Average	Initial	Minimum	Maximum	Final	Daily Average	
1	12.1	0.3	12.8	12.8	5.9	7.2	1.9	26.0	11.6	11.3	17.2
2	1.2	1.6	13.3	13.3	5.5	lost	5.7	66.1	23.0	25.2	30.7
3	2.0	1.1	13.1	12.6	5.5	2.0	1.1	45.5	39.1	14.9	20.4
										72.4	76.7
4	0.6	0.8	16.1	16.1	4.3	2.9	11.2	265.1	123.2	24.0*	28.3*
										72.3	77.2
6	2.1	0.2	14.6	6.8	4.9	2.4	6.7	348.0	51.2	38.0*	42.9*
										45.0	50.0
8	0.9	0.7	12.4	7.8	5.0	166.4†	0.3	102.4	13.9	31.5*	36.5*
9	9.7	0.2	16.4	7.7	7.9	14.1	5.0	131.6	39.8	44.4	52.3
10	14.5	1.6	19.8	13.5	8.7	4.3	7.6	49.4	30.1	19.6	28.3
										382.0	398.1
11	25.6	0.1	33.0	16.6	16.1	21.9	8.0	3,178.1	12.3	26.3*	42.4*
										76.3	83.4
Average.....	7.6				7.1	.....				26.1*	33.2*
										34.5	42.1
	General initial average, urine.....				7.6	General initial average, feces.....				10.0*	17.6*

* Figure corrected. These corrections are based on the absence of corresponding urinary changes, the high excretion being undoubtedly due to some extraneous insoluble form of mercury orally ingested—probably dental amalgam or an old filling. † Not included in average.

TABLE 2.—*Excretion of Metallic Mercury in the Urine and Feces of Human Beings After the Daily Application of One Gram of Two Per Cent Ammoniated Mercury Ointment*

	Urine, Micrograms of Mercury					Feces, Micrograms of Mercury					Total Daily Average
Case	Initial	Minimum*	Maximum*	Final	Daily Average	Initial	Minimum*	Maximum*	Final	Daily Average	
12	0.9	0.8	11.3	0.8	4.9	197.4†	3.4	49.6	7.1	18.0	22.9
13	0.5	0.4	23.5	7.5	6.4	48.7	2.2	15.8	15.8	14.3	20.7
14	6.2	0.0	11.0	11.0	4.9	3.7	1.6	162.1	83.2	30.5	35.4
15	13.8	0.8	24.1	24.1	10.9	4.8	3.5	56.8	16.3	18.8	29.7
16	12.5	1.8	6.1	6.1	5.1	3.0	1.3	22.5	22.5	7.1	12.2
17	7.6	0.4	17.4	17.4	5.8	4.7	4.6	26.5	40.3	16.7	22.5
Average....	6.9	0.7	15.6	11.1	6.3	13.0	2.8	55.5	30.8	17.6	23.9

* Excluding initial determinations. † Not included in average.

The results in table 2 were obtained from a precisely similar experiment except that a 2 per cent ammoniated mercury ointment was used. In this case the final figure of total excretion was 23.9 micrograms, contrasted with the normal 17.6 micrograms. This is within daily variations but represents a possible trivial increase. Moreover, the urinary figure, which mirrors more accurately blood-borne metal, is actually less in this study than the normal, namely, 6.3 and 6.9 micrograms. This definitely does not support the idea of increased absorption of blood-borne metal.

We are able to conclude with reasonable certainty that the unbroken human skin does not permit the absorption of ammoniated mercury at all readily. In this connection, it is interesting to note that calculations made from the work of Sollmann, Cole, Schreiber, De Wolf and Van Cleve [16] show that 1:3,200 of a 50 per cent mild mercurous chloride ointment was absorbed, and this only after a rather vigorous rubbing. These authors also found this material ineffective in the treatment of syphilis, in contrast with the metallic ointment forms.

In the work of Sollmann and his associates it is recorded that eruptions, except those of the follicular type, have little influence on absorption. In fact, we believe that these experienced authors would not lay too much stress on a slight variation, in any case, since occasional accidental ingestion of mercury on the part of the subjects is almost impossible to prevent, as the use of mercury is so widespread and since not inconsiderable amounts are commonly ingested by both man and animals.

However, it seemed of considerable interest to determine by direct experiment if irritation of the skin below blistering levels would influence the course of excretion. Accordingly, we repeated the experiment with the 10 per cent ammoniated mercury ointment several months later with the same subjects but with the additional factor of irritation, which we obtained by submitting the arms of our subjects to the rays of a mercury lamp sufficiently to cause and maintain a generalized erythema. Table 3 shows that such a procedure did not increase the absorption. In fact, the actual excretion of mercury, which was initially somewhat high for some unknown reason (the students were now working in the clinic), all fell during the course of the experiment to the previously determined average figure. We are inclined to think this was more a result of the "training" effect of the experiment, making the subjects mercury conscious, rather than some specific result. We ourselves had become better trained in this matter at the end of this series. These results certainly do not support the often expressed view that oint-

8. Sollmann and others,[16] p. 7.

TABLE 3.—*Excretion of Metallic Mercury in the Urine and Feces of Human Beings After the Daily Application of One Gram of Ten Per Cent Ammoniated Mercury Ointment to Erythematous Skin*

	Urine, Micrograms of Mercury					Feces, Micrograms of Mercury					Total Daily Average
Case	Initial	Minimum	Maximum	Final	Daily Average	Initial	Minimum	Maximum	Final	Daily Average	
1	29.6	9.7	35.1	19.5	18.1	67.3	2.3	93.6	4.5	27.9	46.0
2	21.3	1.7	16.6	1.7	9.6	14.1	2.3	30.2	27.0	15.1	24.7
3	2.9	1.9	38.7	1.9	12.8	25.0	1.3	58.8	12.1	24.6	37.4
8	42.3	6.1	33.0	6.1	18.6	14.8	2.0	44.0	3.8	12.5	31.1
9	53.0	2.3	36.1	4.2	16.5	52.9	13.4	59.5	33.1	49.7	66.2
10	68.8	2.2	50.1	8.3	25.4	31.3	2.6	36.4	6.8	18.2	43.6
	—	—	—	—	—	—	—	—	—	—	—
Average....	36.3	3.9	35.0*	6.9	16.8	34.2	4.0	53.7	14.5	24.6	41.4

* Excluding average of initial determinations.

ments, especially those containing ammoniated mercury, may be much more readily absorbed from erythematous than from normal skin.

We were unable to complete this series by applying ammoniated mercury to the skin denuded of its superficial layers, which would have been exceedingly interesting. Consequently we have no data on this matter, and until such become available it seems wise not to assume that ammoniated mercury cannot be absorbed under such conditions. This view is supported by the fact that orally ingested ammoniated mercury is absorbed by the intestine, at least partially, as shown by renal excretion. The extensive, or prolonged, use of ammoniated mercury on denuded areas of skin is therefore to be regarded as potentially unsafe unless associated with definite steps to prevent contact with the actual living cells (tanning procedures).

Our animal studies show clearly—many loose statements to the contrary—that mercury is not stored anywhere in the body in material quantities. Even after known heavy and prolonged absorption, the total amount of mercury in an animal's body is still less than one fatal dose, were it all instantly mobilized into the blood stream. This fact is also supported by direct analysis of human tissue. We are able to conclude, with justification, that the excretion, and particularly the excretion in the urine, is a good index of the measure of absorption taking place at any given time.

Consequently, we may also conclude, since ammoniated mercury is absorbed so poorly from the unbroken skin, that dangers of general poisoning from this source alone can be considered so slight as to be practically negligible. However, cases of poisoning have been frequently reported from the use of this material on the skin, and we are faced with the problem of harmonizing our work and that of Sollmann and his co-workers on mild mercurous chloride with these facts. The use of any preparation of mercury on a large area of broken skin is probably dangerous. We have recently seen a death associated with the painting of the lower half of a scalded body with mercurochrome. However, we have become acutely aware of a common, almost unpreventable source of danger, namely, oral ingestion. Ointments are messy, and traces readily get onto the fingers and so to the mouth, either directly or, for instance, from a pipe, cigaret or some toy. For animals and babies, we do not believe a practical method exists at the moment to prevent extensive oral ingestion. When one remembers that the oral ingestion of ammoniated mercury is thirty-eight hundred times as effective as cutaneous absorption, as judged by the mercury content of the excreta, the possibilities of poisoning from this source become striking. In consequence, we suggest that the common, but unchecked, belief that the skin of babies absorbs mercury preparations more readily than that of the adult may, in the light of this study, be subjected to a

TABLE 4.—*The Effect of Hot Weather on the Production of Rashes in Human Beings by Ointment Application*

Month	Number of Patients		Number of Applications	Number of Patients with Rashes	Number of Rash Days	Average Mean Temperature, F.	Average Mean Humidity	Treatment	Ratio of Rash Days to Number of Applications
	Treated	New							
September 1939	4	4	48	3	8	80.1	63.7	10% ammoniated mercury ointment	1:6
October 1939	6	2	68	2	3	66.6	68.3	10% ammoniated mercury ointment	1:23
November 1939	5	3	74	2	4	49.8	74.7	10% ammoniated mercury ointment	1:18
December 1939	3	..	27	..	..	46.6	75.0	10% ammoniated mercury ointment	0:27
January 1940	6	6	104	1	1	27.2	79.7	2% ammoniated mercury ointment	1:104
February 1940	6	..	21	..	..	41.2	77.9	2% ammoniated mercury ointment	0:21
February 1940	6	6	56	2	5	41.2	77.9	10% ammoniated mercury ointment plus irradiation	1:11
March 1940	6	..	95	3	8	51.6	70.8	10% ammoniated mercury ointment plus irradiation	1:12
Total.....		21	493	13	29				

* The meteorologic data were officially prepared by the Memphis, Tenn., station of the Federal Weather Bureau.

material alteration. In any case, we believe that the use of any poisonous material on the skin of infants should be associated with serious efforts to prevent oral ingestion.

Our series is not sufficiently large to permit many conclusions concerning the complicated question of the local effects of ammoniated mercury on man. However, as our results were obtained under unusually good experimental conditions, which is not always possible with clinical material, they seem worthy of recording. Moreover, we are able to arrive at two definite conclusions which have some practical interest. Before proceeding, however, it is necessary to state that our working definition of a "rash" was any visible change from the surrounding area. In actual fact none of the rashes we observed ever amounted to more than a few scattered papules, with or without a small patch of erythema, located mainly in the cubital fossa. Some subjects reported (they kept a written record) the occurrence of a rash which was not visible to one of us (O. S. G.) on the next day. These are, however, included in the results (table 4). Two facts are readily discernible from the data. The first is that rashes were much commoner in hot weather. Indeed, even the additional irritation of irradiation caused less effect on the skins of the same persons in February and March than the 10 per cent ammoniated mercury ointment alone had caused in the previous hot September. Secondly, rashes when radiation was not administered tended to appear with the addition of new subjects, that is, early in the experiment. Analysis of these results in more detail shows that most of this visible disturbance comes on within the first week, except in irradiated subjects, which is strongly against the idea of a continuous irritation but supports the view which we definitely hold, that most of these trivial disturbances are due to nonspecific factors. Three patients giving a reaction on one arm were tested with the base alone, and in 2 a similar rash was elicited. In table 4 it may be seen that in hot weather 7 of 9 patients treated with 10 per cent ammoniated mercury ointment had rashes and 2 of 3 treated with the petrolatum base alone had rashes. The average day of onset of the rash was the fourth day. In cold weather 4 of 12 had rashes: 1 treated with the 2 per cent ammoniated mercury ointment and 3 with the 10 per cent ammoniated mercury ointment plus irradiation. The average day of onset of the rash was the fourteenth day. There was one rash day to every seventeen applications.

The prevention of normal evaporation and the gross disturbance occasioned by spreading relatively impervious materials, especially thick pastes, on a skin working under a considerable functional load, as in hot humid weather, in itself is probably the major, if not the sole, cause of these temporary disturbances. These conditions could have been as easily produced by wearing rubber sleeves. Moreover,

the average duration of the rashes for the entire series was merely two and two-tenths days, and under continued application all entirely disappeared. We can probably associate these reactions with the activity of the sweat ducts, especially, as previously mentioned, as none of the animals treated continuously throughout the same period showed any kind of local reaction.

COMMENT

Cardiff [9] recently remarked: "There exists a serious amount of ignorance with reference to the toxicity of arsenate of lead." The reason for this critical statement seems undoubtedly due to the fact that the toxicity of lead arsenate, which has caused an incredible number of reports, has only recently been subjected to sufficiently precise and careful studies from which scientific deductions may be correctly drawn. The same situation seems to exist in regard to mercury, as well as to many other poisons. We have completed the largest series of experiments so far made in one section of this field, but we are fully aware of the fact that we have, in effect, created only a good basis for a much larger series.

SUMMARY AND CONCLUSIONS

The total human excreta normally contain about 20 micrograms of mercury per day.

All foods examined contained mercury except fresh vegetables, eggs and a specimen of crackers.

The constant ingestion of small amounts of mercury is without toxicologic significance.

Applications of 10 per cent ammoniated mercury ointment to the human skin show that approximately 1 part in 3,800 of the mercury applied appears in the total excreta. With 2 per cent ammoniated mercury ointment only traces appear.

The application, even continued, of such ointments to the unbroken skin is not likely to cause general poisoning, providing oral ingestion is strictly prevented.

Some accidental oral ingestion usually occurs in adults and is probably impracticable to prevent in babies and animals.

No experiments were conducted on the application of ammoniated mercury ointment to the broken skin, and the rate of the absorption of ammoniated mercury from such surfaces still remains speculative.

Mild transient erythema and papular reactions are commonly produced by applying ointments to the skin. They occur much more frequently when sweating conditions exist. They are not dependent on the presence of ammoniated mercury in the ointment, being also caused by the base (petrolatum) alone.

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9. Cardiff, I. D.: J. Indust. Hyg. & Toxicol. **22**:333, 1940.

SULFAGUANIDINE IN THE TREATMENT OF PROCTITIS DUE TO LYMPHO-GRANULOMA VENEREUM

REPORT OF SIX CASES

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The most serious complication of lymphogranuloma venereum observed is cicatrizing proctitis, which up to the present time has defied all methods of therapy. In some cases of this condition there has been improvement from thermal response obtained by the intravenous injection of Frei antigen, and recently promising results have been reported due to the efficacy of sulfanilamide and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) in these cases. Such therapeutic methods, however, are of value in a limited number of cases. It occurred to one of us (O. C.) that sulfaguanidine (sulfanilylguanidine), because of its specific action on the intestinal tract, might be of value.

Sulfaguanidine is a guanidine derivative of sulfanilamide which is characterized by its lack of absorbability in the gastrointestinal tract. This property permits one to obtain a relatively high effective concentration of the drug in the intestines, and thus the bacteriostatic action of the drug can be utilized here. Because of its poor absorption, few systemic toxic manifestations are to be expected. Its administration has proved to be useful [1] in the treatment of enteric infections, such as acute bacillary dysentery, and as a preoperative and postoperative measure with surgical therapy of the intestinal tract.

From the Department of Dermatology and Syphilology of the Third (New York University) Medical Division, Bellevue Hospital, service of Dr. Frank C. Combes.

1. (*a*) Marshall, E. K., Jr.; Bratton, A. C.; White, H. J., and Litchfield, J. T., Jr.: Sulfanilylguanidine: A Chemotherapic Agent for Intestinal Infections, Bull. Johns Hopkins Hosp. **67**:163, 1940. (*b*) Marshall, E. K., Jr.; Bratton, A. C.; Edwards, L. B., and Walker, E.: Sulfanilylguanidine in Treatment of Acute Bacillary Dysentery in Children, ibid. **68**:94, 1941. (*c*) Lyons, G. M.: Chemotherapy in Acute Bacillary Dysentery: II. Clinical Use of Sulfanilylguanidine, West Virginia M. Monthly **37**:54, 1941. (*d*) Fournier Villada, R., and Laguna, J.: La sulfaguanidina en las disenterías bacílares, Prensa méd. mex. **6**:98, 1941.

In our study 6 patients with proctitis due to lymphogranuloma venereum were treated with sulfaguanidine, 24 Gm. daily (four doses of 6 Gm.), for from twenty-seven to forty-seven days. In all the patients with simple proctitis subjective and objective improvement was noted. The latter was revealed by repeated proctoscopic examinations. The best results were obtained in patients with simple proctitis. No improvement was noticed in patients with narrow fibrotic stricture of the rectum; the drug was given to them as a preparatory measure before surgical intervention. It is not to be expected that chemotherapy will do more than heal erosions and ulcerations. It will not act on the fibrous tissue.

The excellent results obtained prompt us to make this preliminary report.

REPORT OF CASES

CASE 1.—T. L., a white man aged 52, was admitted to Bellevue Hospital on March 24, 1941, complaining of rectal discharge and severe constipation. He gave a history of an untreated penile lesion in 1907. He stated that he had never had inguinal buboes. Fourteen months prior to entry he noted a painful, solid swelling of the right buttock close to the anal orifice. This developed slowly for thirteen months. Surgical drainage was effected, and in the process the rectal sphincter was cut. The patient had had painful defecation with blood and pus in the stools for two years previous to the operation. During this period he had occasional diarrhea alternating with constipation.

During the months prior to hospitalization he received a course of treatment with sulfathiazole, totaling 18.18 Gm., an eight day course of sulfanilamide therapy, totaling 36 Gm. of the drug, and a 12 day course of intravenous injections of mouse brain antigen (the injections being given every third day). No improvement had been noted subjectively or proctoscopically from these therapeutic measures.

Physical examination gave essentially negative results except for revealing a gaping incision 3 inches (7.5 cm.) long extending through the anal sphincter and laterally into the perineal musculature. This V-shaped incision was covered with a foul-smelling yellowish green pus, and from the apex of this incision a sinus extended into the rectum. Proctoscopic examination showed an edematous, eroded, ulcerating and bleeding mucosa for a distance of 8 cm. from the anal orifice. No stricture was present.

The Wassermann reaction of the blood was negative. The reaction to an Ito-Reenstierna test was negative. Intradermal Frei tests performed with mouse brain antigen, with lygranum (chick embryo antigen) and with a human antigen elicited positive reactions. The blood protein content was 7.8 Gm., with 3.8 Gm. of albumin and 4 Gm. of globulin, per hundred cubic centimeters.

He was given 24 Gm. of sulfaguanidine daily (6 Gm. four times a day) for thirty-one days. Weekly sulfaguanidine levels in the blood were 4.41 mg., 4.32 mg. and 1.82 mg. per hundred cubic centimeters. No toxic symptoms were noted.

Two weeks after therapy was begun the proctologist reported that the rectal mucosa was showing evidence of repair with diminution of the amount of blood and pus and with epithelization of many of the previously denuded areas. This improvement continued, and at the end of thirty-one days the rectal mucosa was normal, except for the depression caused by the opening of the sinus. The

perineal incision was clean and granulating but was declared by the surgeons to be too gaping for healing to be expected. The patient had gained 23 pounds (10.4 Kg.) under this therapy and had had no rectal discomfort after the second week. He refused surgical repair of his incision and was discharged to the outpatient department. One month later he reported that he was still free of rectal discomfort and protoscopic examination again failed to show any pathologic changes of the rectal mucosa.

CASE 2.—E. T., a 35 year old woman, entered Bellevue Hospital on Feb. 8, 1941, complaining of bloody, purulent rectal discharge. The patient stated that twelve years previously she had received "injections in the arm" after the reaction to a Frei test was found to be positive. She received another course in 1934. No subjective improvement was noted from these injections, and during these years she experienced intermittent diarrhea associated with the passing of blood and pus. Rectal discomfort had been specially severe during the last three years. She gave a history of an unrepaired tear during childbirth in 1923.

Physical examination gave essentially negative results. Rectal examination disclosed complete disappearance of the rectovaginal septum for the lower 2 inches (5 cm.) of these cavities. The rectal mucosa was ulcerated and bleeding for a distance of 7 cm. The rectum was narrowed to the diameter of a lead pencil. There were several perianal tabs, one of which bridged from one buttock to the other.

The Wassermann reaction of the blood was anticomplementary. The reaction to an Ito-Reenstierna test was negative. Reactions to intradermal Frei tests with mouse brain antigen, with lygranum (chick embryo antigen) and with human antigen were positive. The total protein content of the blood was 10.7 Gm. per hundred cubic centimeters, with 3.2 Gm. of albumin and 7.5 Gm. of globulin.

Soon after entry she was given sulfathiazole, but its administration was discontinued when arthralgia and myalgia developed, with a temperature of 104 F. Twelve days later sulfaguanidine, 24 Gm. daily (6 Gm. four times a day), was given for twenty-eight days. Sulfaguanidine levels in the blood at weekly intervals were 3.6 mg., 2.89 mg. and 2.4 mg. per hundred cubic centimeters.

Weekly proctoscopic examinations showed beginning improvement after the second week, and at the end of the twenty-eight days the proctologist considered the patient in "excellent condition with a completely healed mucosa" and recommended surgical procedures for her stricture.

She gained 16 pounds (7.3 Kg.) while in the hospital and had no rectal discomfort during the last two weeks of her therapy. No toxic symptoms were noted.

CASE 3.—L. B., a Negress aged 26, was admitted to Bellevue Hospital on May 12, 1941, complaining of constipation, painful defecation and purulent rectal discharge of about one year's duration. During this time she had occasional periods of diarrhea associated with the passage of blood and mucus. No history of inguinal adenopathy was obtained. Two months prior to entry the patient had a painful swelling of the right ankle, which subsided after about three weeks, only to be followed by swelling of the wrists and elbows, which was present on admission.

Physical examination gave essentially negative results except for a slight swelling of both wrists and elbows. Proctoscopic examination revealed a partially fibrotic band about 2 inches (5 cm.) from the anal opening. The rectal mucosa was edematous, eroded in many areas, and bled easily on trauma. The process extended to about 6 cm. from the anal orifice.

The Wassermann and Kahn reactions of the blood were negative. The reactions to intradermal Frei tests performed with mouse brain antigen, lygranum (chick embryo antigen) and human antigen were positive. The first two antigens injected intravenously elicited a febrile response. The total protein content of the blood was 8.6 Gm. per hundred cubic centimeters, with 5.1 Gm. of albumin and 3.5 Gm. of globulin.

Sulfaguanidine was given in amounts of 24 Gm. daily (6 Gm. four times a day). Within one week the patient stated that her bowel movement was easier. Seventeen days after therapy was begun the mucosa was more nearly of normal color, oozed less blood and showed evidence of healing. The last proctoscopic examination revealed the mucosa to be of normal appearance and the ulcerations healed. The partially fibrotic band was unchanged.

The patient gained 12 pounds (5.4 Kg.) while under treatment and when discharged had no rectal discomfort. She received sulfaguanidine for forty-seven days. No toxic symptoms were noted. The sulfaguanidine level of the blood never exceeded 3.7 mg. per hundred cubic centimeters.

Case 4.—G. W., a Negress aged 28, was admitted to Bellevue Hospital on May 14, 1941, complaining of rectal discharge and constipation of three years' duration. No history of inguinal adenopathy could be elicited. She had noted occasional blood in the stool during this time.

The results of physical examination on admission were essentially negative. Proctoscopic examination showed an extensive ulceration of the lower and middle third of the rectum, with partial stricture. Intradermal Frei tests performed with three different antigens elicited positive reactions. The intravenous injection of these also elicited a febrile response. The Wassermann reaction of the blood was negative.

Sulfaguanidine was given for forty-five days, 24 Gm. daily (6 Gm. four times a day). At the end of three weeks proctoscopic examination showed a decided improvement; the mucosa was smooth, and the ulcerations were for the most part healing. The purulent discharge was no longer present. A few days before the patient's discharge from the hospital another proctoscopic examination showed the mucosa to be smooth and of normal color, the ulcerations being entirely healed. A fibrotic ring was still present about 8 cm. from the anal opening, but the finger could pass. No toxic symptoms were noted. The sulfaguanidine level in the blood the third week of treatment was 3.9 mg. per hundred cubic centimeters.

Case 5.—M. B., a Negress aged 34, was admitted to Bellevue Hospital because of constipation and bloody, purulent rectal discharge of two years' duration.

The Wassermann reaction of her blood was negative. Intradermal Frei tests performed with mouse brain antigen, with lygranum (chick embryo antigen) and with human antigen elicited positive reactions. Physical examination gave essentially negative results. Proctoscopic examination showed several ulcerations of the lower third of the rectum, the mucosa being edematous. A fibrotic stricture was present at about 8 cm. from the anal opening.

Sulfaguanidine was administered in amounts of 24 Gm. daily (6 Gm. four times a day). The patient felt better after the second week. A proctoscopic examination at the beginning of the third week showed that the ulcerations were healing and that the stricture was unchanged. The patient was unable to stay longer in the hospital and was discharged after seventeen days of treatment. She was given enough tablets to carry on the treatment at home for two weeks.

She reported weekly for two weeks to the outpatient department and stated that she felt much better and that though she was still constipated her rectal discharge had disappeared.

CASE 6.—P. A., a white man aged 40, was admitted to Bellevue Hospital on June 11, 1941 because of constipation and rectal discharge of many years' duration. He stated that he was operated on for hemorroids ten years previously, without improvement. During the last year the discharge had become profuse. The Wassermann reaction of his blood was negative. The reaction to a Frei test was positive. Physical examination gave essentially negative results. Proctoscopic examination showed a firm narrow annular stricture 4 cm. from the anal margin. The mucosa was pale pink and around the stricture had a small nodular appearance and bled easily. The mucosa above and below the stricture was ulcerated. There was fissuring and laceration of the posterior anal margin which was covered with purulent discharge.

Sulfaguanidine was given, 24 Gm. daily (6 Gm. four times a day), for twenty-seven days. A proctoscopic examination performed before the patient's discharge from the hospital showed definite improvement of the process, but the stricture was still present. Rectal discomfort had disappeared but constipation was still severe.

SUMMARY AND CONCLUSIONS

Sulfaguanidine was used for treatment in 6 cases of proctitis due to lymphogranuloma venereum. In all the cases of inflammatory proctitis subjective and objective improvement was noted. The latter was revealed by repeated proctoscopic examination. No improvement was noted in cases of fibrotic stricture of the rectum. In these cases sulfaguanidine should be used as a preoperative measure.

Sulfaguanidine, because of its immediate effect on the rectal lesions, is of value in the treatment of proctitis due to lymphogranuloma venereum.

NOTE.—Since this article was submitted for publication 4 additional patients have been treated with satisfactory results. Three of them received the drug as a preoperative measure.

The sulfaguanidine used in this study was supplied by E. R. Squibb and Sons.

Dr. Huppert and his associates performed the proctoscopic examinations.

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ACCIDENTAL INOCULATION WITH SPIROCHAETA PALLIDA

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One of the hazards connected with clinical and experimental studies on syphilis is the possible accidental inoculation of the worker with Spirochaeta pallida. A physician who treats syphilis or who handles syphilitic animals is liable to be inadvertently stuck, scratched, bitten or in other ways contaminated with spirochetes. The literature contains several reports of such accidents with organisms obtained from both human and animal sources. However, there have been no published reports of instances in which there was reasonable certainty that spirochetes from an experimental animal had entered the body but in which actual infection did not subsequently occur.

In the case to be reported accidental injection of S. pallida probably did take place without the dissemination of the organisms and frank syphilis ensuing. In addition to this report, a summary of current opinion as to the procedure of choice in the event of such an accident is recorded.

REPORT OF A CASE

In February 1938 I accidentally stuck my finger with a needle to a depth of approximataely 1/16 inch (0.16 cm.) while aspirating an active testicular syphiloma in a rabbit inoculated with the Nichols strain of S. pallida. The wound was allowed to bleed freely, and during this time an examination of the aspirated material remaining in the needle revealed 8 to 10 spirochetes per oil immersion field. The finger and hand were immediately thoroughly rubbed with 33 per cent mild mercurous chloride ointment, and a rubber finger cot filled with mild mercurous chloride was placed over the finger for ten hours. No intravenous or intramuscular injections were given at any time.

Several Kolmer Wassermann and Kahn tests of the blood prior to the accident had given negative results. Kolmer Wassermann and Kahn reactions one hour after the accident were negative. A base line physical examination with roentgen ray and fluoroscopic examination of the heart showed no abnormalities. Tests of the blood were repeated at weekly intervals for ninety days, after which they were repeated at three to six month intervals to the present. The site of the injection, skin, mucous membranes and glands were examined frequently for clinical signs of syphilis. A roentgenogram of the chest in November 1940 showed no changes in the appearance of the heart and aorta. Examination of the spinal fluid was not made. During the entire period of observation there was no clinical or laboratory evidence of syphilis.

With the follow-up study described, it is reasonable to assume that despite a probable inoculation with the causative organism, syphilis did not develop.

Ever since the transmission of syphilis from man to the rabbit, there has been the question of whether S. pallida has become attenuated or lost its virulence for man during long residence in the body of the experimental animal. A number of reports in the literature reveal that the animal-harbored spirochete has not lost its ability to infect man.[1] Wakerlin [2] reported an instance of accidental infection from a rabbit with a strain of organisms (Nichols) which had been carried in rabbits for thirteen years. On the other hand, there are capable syphilologists who feel that a strain which has been through repeated animal transfers loses its virulence for man. S. S. Greenbaum [3] cited the instance of a laboratory worker who had worked with the Nichols strain of S. pallida for almost twenty years. She had jabbed her fingers innumerable times with needles pregnant with syphilitic emulsified rabbit testicle. She had aspirated such material into her mouth, and it had sprayed, also accidentally, into her eyes. For the mouth and eyes all she used subsequently was saline solution wash. The Kolmer Wassermann reactions of her blood were persistently negative. This is an extremely important consideration from the standpoint of what is to be done to the person who accidentally receives the organisms into his body. The reports of Wakerlin and others are so convincing that it must be assumed that despite long residence in the experimental animal the Nichols strain and possibly other strains of the organism are capable of infecting man.

In the instance herein reported no antisyphilitic drugs (arsenicals or heavy metals) were injected as a prophylactic measure. The wound was allowed to bleed freely, and the mild mercurous chloride ointment was vigorously applied. The reason for this method of handling the situation will be briefly discussed. One of the cardinal rules of syphilology is that treatment for syphilis should not be given until a diagnosis of the disease has been positively established. Once specific treatment is instituted, the picture becomes masked, so that there is the eternal question as to whether or not syphilis ever existed. It was felt that if antisyphilitic treatment was started, it should be continued as if the case were one of proved syphilis. In other words, abortive treatment would be a halfway measure which would confuse the picture as

1. Metchnikoff, E., and Roux, E.: Etudes expérimentales sur la syphilis. Cinquième mémoire, Ann. Inst. Pasteur **20**:785, 1906. Buschke, A.: Ueber die Beziehung der experimentell erzeugten Tiersyphilis zur menschlichen Lues, Deutsche med. Wchnschr. **60**:1783, 1913. Graetz, F., and Delbanco, E.: Beiträge zum Studium der Histo-Pathologie der experimentellen Kaninchensyphilis, Med. Klin. **10**:420, 1914. Levaditi, C., and Marie, A.: Etude sur le tréponème de la paralysie générale, Ann. Inst. Pasteur **33**:741, 1919. Grahylle, D.: Le lapin atténue-t-il la virulence, pour l'homme, du tréponème pâle? Compt. rend. Soc. de biol. **91**:911, 1924

2. Wakerlin, G. E.: Laboratory Infection in Man by the Spirocheta Pallida of Experimental Rabbit Syphilis, J. A. M. A. **98**:479 (Feb. 6) 1932.

3. Personal communication to the author.

it would in a case of actual syphilis. On the other hand, it was felt that application of a potent spirocheticidal substance, such as mild mercurous chloride, directly to the site of inoculation would kill or attenuate any organisms that might have been deposited. In the event that syphilis did develop, it would have been detected early and with proper treatment could have been cured. This alternative was believed to be more reassuring than the prospect of never knowing whether or not syphilis had ever been present.

In order to secure the valuable opinion of eminent authorities in the field, a questionnaire was addressed to a number of syphilologists. As was to have been expected, there was considerable difference of opinion as to the procedure of choice in the event of an accident such as the one described. Many syphilologists had had no similar experience and did not choose to render an opinion. But among those who did state a definite opinion, the choice of whether to give arsenicals and heavy metals or to employ mild mercurous chloride with watchful waiting was about equally divided.

Thus, J. H. Stokes,[8] stated: "So far as the procedure of choice under such circumstances as described is concerned, I can say only that I have grown farther and farther away from the idea of giving any form of systemic treatment for syphilis as a prophylactic. Laying the inoculation site open as completely as possible to the local action of appropriate mercurials seems to me to be the procedure of choice."

M. Severac [8] stated the belief that "a local antiseptic such as metaphen, which is a mercurial, should be used. In my opinion, no treatment with arsenicals or bismuth should be given, as this abortive treatment will obscure the clinical picture, which will always leave a doubt whether or not infection took place."

Likewise, J. A. Kolmer [8] stated: "On such occasions I am greatly opposed to intravenous injections of arsphenamine or intramuscular injections of a bismuth compound, because I think it is much better to keep the subject under observation for at least eight weeks. My thought has been that if treatment is given for prophylactic purposes it would forever obscure the question of syphilitic infection. During the past fifteen years I have been consulted by twelve physicians who accidentally pricked their fingers while treating patients with acute early syphilis, during which time their blood came into contact with the puncture wound. In each instance I advised encouraging free bleeding, followed by daily application of 33 per cent mild mercurous chloride ointment for three or four days. In no instance did infection follow."

J. E. Kemp,[8] E. Hoffman,[8] P. D. Rosahn,[8] S. B. Frank [8] and A. Rule [8] expressed similar opinions.

On the other hand, P. J. Hanzlick [8] stated the following belief: "While mild mercurous chloride has long been regarded as a satisfac-

tory agent for local application, I do not put the same confidence in it as apparently others do. I use tincture of iodine for any scratches or abrasions, as it is a more powerful antiseptic and the iodine penetrates deeper into tissues than does mild mercurous chloride. The next step would be intravenous injection of arsphenamine in case a local lesion is suspected of contamination by the virus."

S. W. Becker [3] stated: "I believe that in the case of possible accidental injection with S. pallida, the patient should be given three intravenous injections of arsphenamine, or a comparable arsenical, in five days, provided the patient is seen up to forty-eight hours after possible injection."

J. F. Mahoney [3] reasoned thus: "It is realized that the use of arsenic is considered to be dangerous because of the possibility of subcurative therapy leading to a symptomless invasion. If the experimental work which has been done here in the field of prophylaxis is correct, it seems to point to the fact that the prophylactic value of mercury is dependent on its systemic spirocheticidal action. It is thus in the same category as arsenic, and its use is attended by exactly the same dangers as arsenic. Mercury has a possible advantage of having a slow rate of absorption and elimination, thus exerting its protective action over a longer period. This advantage is probably offset by the fact that the administration of a drug by inunction is an extremely haphazard procedure. The amount of mercury absorbed is dependent on the preparation itself and on the thoroughness with which the ointment is rubbed into the skin. It does not permit of an accurate scaling of dosage. Hence, the dangers being equal, the more exact procedure seems to be preferable."

U. J. Wile,[3] C. K. Hu,[3] K. K. Bryant [3] and F. Blumenthal [3] also expressed the opinion that arsenicals are indicated.

Greenbaum's [3] choice depended on the circumstances: "When a needle has contacted a person with chronic syphilis, I believe that your procedure is certainly sufficient. When the needle has just been used for withdrawal of blood from a person with acute florid syphilis, I would strongly advise the simultaneous injection of three doses of neoarsphenamine and three doses of a bismuth compound, spaced as closely as possible."

COMMENT

The aggregate experience of these and other syphilologists covers at least 25 cases in which supposedly syphilitic material was accidentally injected. In no instance, regardless of whether mild mercurous chloride or arsphenamine was employed, did syphilis ensue.

There can be no question that inoculation with S. pallida may occur without subsequent infection. At least the organisms reach the surface of the skin and have the opportunity to enter. It would be difficult to believe that every exposure to infectious material leads to a

transfer of the infection to the exposee. As Stokes [3] pointed out, to define the condition under which this does and does not occur is a problem of extraordinary difficulty.

The efficacy of 33 per cent mild mercurous ointment as recommended by Metchnikoff and Roux has been proved repeatedly, particularly in the Army and Navy personnel. It is generally conceded that such a preparation should be used in the case of sexual exposure to infection and that arsphenamine and bismuth should not be given as a prophylactic measure. It is also true that prophylaxis with mild mercurous chloride is not uniformly efficacious, yet that does not detract from its value and continued usage.

Apparently the strongest argument in favor of using mild mercurous chloride and watchful waiting in instances of accidental inoculation is that this drug exerts a spirocheticidal action on those organisms on the surface of the skin and at the same time keeps the picture free from any camouflaging, such as might be introduced by the use of abortive arsenical therapy.

SUMMARY AND CONCLUSIONS

A case is reported of probable accidental inoculation of a person with the Nichols strain of S. pallida without subsequent development of syphilis. In this instance the wound was allowed to bleed freely and 33 per cent mild mercurous chloride ointment was applied. No arsenicals or heavy metals were administered. A serologic follow-up study showed no evidence of infection.

A canvass of the opinions of some outstanding syphilologists reveals a difference of opinion as to the procedure of choice in the case of accidental inoculation with S. pallida. Approximately half of them stated that mild mercurous chloride together with watchful waiting was the treatment of choice, whereas the other half expressed the opinion that prophylactic injections of arsenicals and heavy metals were indicated. In a collective experience of at least 25 such accidents, syphilis did not develop in a single instance regardless of whether mild mercurous chloride or arsphenamine prophylaxis was used.

The Nichols strain of S. pallida has been shown to have retained its virulence for man after repeated rabbit transfers over a period of thirteen years.

It is recommended that injections of arsphenamines and bismuth be withheld in cases of accidental inoculation until a positive diagnosis of syphilis has been established and that free bleeding and the local application of 33 per cent mild mercurous chloride ointment be employed at the time of the accident. Frequent tests of the blood should be made during the observation period, which should cover at least a ninety day interval.

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HISTAMINE IN TREATMENT OF ATOPIC DERMATOSES

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The difficulties of the specific immunologic approach to the investigation and treatment of the cutaneous manifestations of atopy are such that any other approach which offers any hope of simplifying the problem is deserving of thorough study. The theory of Dale and Laidlaw [1] seemed to offer some such hope. These authors, in 1918, advanced the theory that the allergic reaction is brought about by contact of specific allergens and antibodies in the tissue cells with liberation of histamine and that the histamine itself is responsible for the dilatation and increased permeability of the capillaries. This explanation seems to have been rather generally accepted. It is not certain, however, that the substance released in the tissues is actually histamine, and Lewis and Grant [2] suggested the term "histamine-like" or "H substance" as a better designation. The explanation of allergy proposed by Dale and Laidlaw suggested the possibility of inducing hyposensitization or increased tolerance by repeated injections of a small amount of histamine solution. Histamine therapy was applied for a time and then practically abandoned, but for several years it has again attracted the attention of dermatologists and allergists. Reports as to the value of histamine therapy are conflicting, and there is little in the literature concerning its use in the treatment of dermatoses other than urticaria and angioneurotic edema.

The mechanism of the action of histamine in therapy is not fully understood. Two possibilities suggest themselves: (*a*) gradual increase in tolerance to the H substance in a way comparable to that induced by specific antigens and vaccines and (*b*) stimulation of production of the enzyme histaminase and consequent inactivation of the histamine liberated in the tissues. The latter has been suggested by Elliott [3]

Read at the Sixty-Fourth Annual Meeting of the American Dermatological Association, Inc., New Orleans, April 7, 1941.

1. Dale, H. H., and Laidlaw, P. P.: Histamine Shock, J. Physiol. **52**:355 (March) 1919.

2. Lewis, T., and Grant, R. T.: Vascular Reactions of Skin to Injury: Liberation of a Histamine-Like Substance in Injured Skin, Heart **11**:209 (May) 1924.

3. Elliott, R. W., in discussion on Alexander and Elliott,[4] J. A. M. A. **114**: 522 (Feb. 10) 1940.

as the probable mode of action of the histamine administered intravenously by Alexander and Elliott.[4] Fühner[5] found that refractoriness to histamine could be induced in animals by repeated injections of increasing doses of the substance. Farmer[6] observed that strips of uterine muscle from guinea pigs which had been treated with increasing doses of histamine were less sensitive to histamine than the uterine muscle of guinea pigs not so treated. On the other hand, Maisel and Abramson[7] found that patients who were given rather large doses of histamine over a period of more than a month showed no evidence of any change in sensitiveness to histamine at the end of that time.

Alexander[8] made the observation that allergic symptoms due to specific extrinsic allergens are not influenced by treatment with histamine and that the patients who obtain relief are those in whom no extrinsic allergens can be identified and whose conditions are presumably due to an intrinsic cause, probably H substance.

Encouraging results reported on the use of histamine therapy in certain nondermatologic conditions of allergic or suspected allergic origin have stimulated investigation of its value in dermatologic diseases of similar origin. Among these nondermatologic reports mention should be made of the work of Thiberge[9] on asthma and hay fever, of Shelden and Horton[10] on Ménière's disease, of Horton[11] on erythromelalgia of the head or vascular headache and of Farmer[12] on vasomotor rhi-

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4. Alexander, H. L., and Elliott, R. W.: Treatment of Chronic Urticaria with Intravenous Injections of Histamine, J. A. M. A. **114**:522 (Feb. 10) 1940.

5. Fühner, H.: Das Pituitrin und seine wirksamen Bestandteile, München. med. Wchnschr. **59**:852, 1912.

6. Farmer, L.: Non-Specific "Desensitization" Through Histamine, J. Immunol. **36**:37 (Jan.) 1939; Experiments on Histamine-Refractoriness: Non-Specific "Desensitization" Through Oral Application of Histamine, ibid. **37**:321 (Oct.) 1939.

7. Maisel, F. E., and Abramson, H. A.: Quantitative Measurement of Whealing in Hypersensitiveness to Cold Treated with Histamine and Histaminase, J. Allergy **12**:6 (Nov.) 1940.

8. Alexander, H. L.: Treatment of Allergic Disorders with Histamine and Histaminase, J. Lab. & Clin. Med. **26**:110 (Oct.) 1940.

9. Thiberge, N.: Histamine and Typhoid Protein Compared in the Control of Asthma and Hay Fever, J. Allergy **6**:282 (March) 1935.

10. Shelden, C. H., and Horton, B. T.: Treatment of Ménière's Disease with Histamine Administered Intravenously, Proc. Staff Meet., Mayo Clin. **15**:17 (Jan. 10) 1940.

11. Horton, B. T.: The Use of Histamine in the Treatment of Specific Types of Headaches, J. A. M. A. **116**:377 (Feb. 1) 1941.

12. Farmer, L.: The Histamine Treatment of Allergic Diseases, J. Lab. & Clin. Med. **26**:802 (Feb.) 1941.

nitis and asthma. The results reported seem to justify some hope that comparable results might be obtained in the dermatoses which are thought to have an atopic basis.

Saylor and Wright [13] reported a case in which urticaria due to sensitivity to cold improved in response to histamine injected intradermally at first and later subcutaneously as larger doses were reached. This result has been duplicated by other observers in cases of physical allergy.

Alexander and Elliott treated 14 patients with chronic urticaria with histamine administered by the intravenous drip method. Eleven of them obtained prompt and complete remission. Improvement was also noted in another series of patients treated by subcutaneous injections of histamine, although the results were less striking.

Porch [14] recently employed histamine in treating 53 patients with atopic dermatoses, including 30 with urticaria alone, 22 with urticaria and angioneurotic edema and 1 with pruritus. Forty patients were entirely relieved; in 11 the condition was decidedly improved, and 2 were not benefited.

TOXIC REACTIONS FROM HISTAMINE

Toxic symptoms occasionally develop during histamine therapy. Headache, nervousness, dizziness, coughing and choking, flushing and cyanosis should be watched for, but they seldom occur during intradermal or subcutaneous injections of histamine. During intravenous administration a moderate flushing, particularly of the face, and a little headache usually occur. These symptoms are relieved quickly by epinephrine but can usually be controlled by regulating the rate of drip of the histamine solution.

METHODS OF TREATMENT

Histamine has usually been administered intradermally or subcutaneously and at intervals varying from a day or even less to two or three days and later in the course of treatment at intervals of a week or more. Alexander stated that histamine, to be effective, should be given every day, or twice a day at first, and later two or three times a week. There is a tendency at present to plan the dosage after the pattern of specific desensitization, that is, to begin with a dilute solution and a small dose and slowly increase the dose and later the concentration. Considerable experience will be necessary before the technic

13. Saylor, L. L., and Wright, I. S.: Studies on Two Cases of Urticaria from Cold Sensitivity and of the Effect of Histamine Treatment, Am. J. M. Sc. **192**:388 (Sept.) 1936.

14. Porch, L. D.: Histamine Therapy in Allergy, J. Lab. & Clin. Med. **26**:499 (Dec.) 1940.

can be standardized as to the proper initial dose and the proper rate of increase for the best results.

Fiessinger and Gajos [15] introduced histamine into the skin by iontophoresis, but this method has not been popular.

For the intravenous administration of histamine, Alexander and Elliott used a dilute solution and gave it by means of a slow drip on successive days. They used histamine base. They encountered no troublesome reactions. Horton [16] during 1940 gave one thousand, two hundred and seventy-two intravenous injections of histamine without any acute histamine shock or any untoward symptoms. It is fair to assume, then, that this method of administration is relatively safe.

In the series of cases reported here histamine has most often been given intradermally until the larger doses were reached, and these were given subcutaneously. In children and in some very nervous persons the subcutaneous route was used from the beginning. Ten patients have received histamine intravenously, and forty-seven such treatments have been given. The solution for intradermal and subcutaneous use contained 2.75 mg. of histamine phosphate per 5 cc. of physiologic solution of sodium chloride and was further diluted as desired. The solution for intravenous injection contained 5.5 mg. per 500 cc. of the saline solution and was used in that strength. The intradermal and subcutaneous injections were given at intervals of one to three days. Various dilutions and doses were employed in beginning the treatment. The intravenous treatments were usually given daily for from two to eight injections. Some patients were given a course of three daily intravenous injections with the course repeated after several days. The intravenous treatment was sometimes preceded by a number of intradermal injections and was usually succeeded by further such treatment. The usual rate of administration was 30 to 40 drops per minute.

RESULTS OF TREATMENT

Included in this paper are the reports of 11 cases of chronic urticaria, angioneurotic edema and pruritus with dermographia but no spontaneous whealing and of 11 cases of classic atopic dermatitis. Two cases of prurigo mitis are included because some observers have considered this disease to have an atopic background. One case of generalized pruritus and 1 of pruritus ani in which the conditions were strongly suspected of being of an allergic nature are added to the report. The cases are presented in tabular form.

15. Fiessinger, N., and Gajos, A.: Urticaire et histamine, Paris, Vigot Frères, 1937.

16. Horton, B. T.: Ménière's Disease and Histamine, J. A. M. A. **116**:646 (Feb. 15) 1941; The Use of Histamine in Ménière's Disease, Surg., Gynec. & Obst. **72**:417 (Feb. 15) 1941.

Of the 11 patients with urticaria, all were apparently benefited by histamine therapy, the degree of improvement ranging from 40 per cent to complete relief. Two were completely relieved by intradermal treatment alone, and 2 were improved from 50 to 75 per cent by intradermal injections. Three patients were relieved of all whealing after the first intravenous injection, and the slight pruritus remaining responded either to further intravenous injections or to intradermal injections

TABLE 1.—*Results of Histamine Therapy in Patients with Urticaria*

Patients	Diagnosis	Method of Administration	No. of Injections	Dose and Solution	Results
W. J. S.	Chronic papular urticaria	Intravenous	3	60-150 cc.	Cured *
C. L. B.	Chronic urticaria	Intravenous	3	50-140 cc.	Cured (after one intravenous injection)
		Intradermal	8	0.1 cc. (1:2,000)	
S. R.	Chronic urticaria	Intravenous	3	50-150 cc.	Cured (after one intravenous injection)
		Intradermal	5	0.1-0.2 cc. (1:2,000)	
E. W.	Chronic urticaria and angioneurotic edema	Intravenous	3	50-125 cc.	Cured (after one intravenous injection)
		Intradermal	8	0.02-0.2 cc. (1:2,000)	
J. C.	Chronic urticaria	Intradermal	25	0.05 cc. (1:50,000) —0.2 cc. (1:2,000)	Improved approximately 40 per cent
		Intravenous	6	50-125 cc.	
R. G.	Chronic urticaria	Intradermal and subcutaneous	18	0.1 cc. (1:100,000) —0.35 cc. (1:2,000)	Improved approximately 50 per cent
		Intravenous	6	50-175 cc.	
J. M.	Chronic urticaria	Intravenous	7	50-175 cc.	Eventual relief, approximately 50 per cent
		Intradermal	20	0.02-0.1 cc. (1:2,000)	
J. D. S.	Chronic urticaria	Intradermal	14	0.04-0.12 cc. (1:2,000)	Improved approximately 75 per cent
W. L. D.	Chronic urticaria	Intradermal	3	0.05-0.1 cc. (1:100,000)	Improved 50 per cent (left town; no report)
J. G.	Chronic urticaria	Intradermal	19	0.05-0.12 cc. (1:2,000)	Cured
R. C. W.	Pruritus with dermographia	Intradermal	28	0.05 cc. (1:5,000) 0.2 cc. (1:2,000)	Cured

* The word cured indicates freedom from symptoms during the period in which I was able to follow the results of treatment (from one to three months).

which were given subsequently. Another patient responded to three intravenous injections alone, and in 3 patients only 40 to 50 per cent improvement could be obtained even after prolonged treatment with intradermal, subcutaneous and intravenous injections of histamine.

Of 11 patients with atopic dermatitis reported on, only 3 obtained any benefit which could be attributed to the effect of the histamine, and this improvement varied from 25 to 90 per cent. The person who obtained the greatest improvement failed to respond to histamine during an exacerbation the following year. The remaining 8 patients

received no benefit whatever. The 3 patients with dermatitis who received histamine intravenously apparently were not benefited by that procedure, although 1 received eight injections.

TABLE 2.—*Results of Histamine Therapy in Patients with Atopic Dermatitis*

Patients	Atopic Dermatitis	Method of Administration	No. of Injections	Dose and Solution	Results
C. G.	Flexural	Intradermal	10	0.01-0.25 cc. (1:2,000)	No benefit
H. S.	Flexural	Intradermal	10	0.04-0.2 cc. (1:2,000)	No benefit
H. L.	Generalized	Intradermal	8	0.03-0.12 cc. (1:2,000)	No benefit
D. S.	Flexural	Subcutaneous	13	0.02-0.3 cc. (1:2,000)	Improved 75 per cent
F. H.	Flexural	Subcutaneous	8	0.02-0.2 cc. (1:2,000)	No benefit
E. G.	Flexural	Intradermal	8	0.02-0.1 cc. (1:2,000)	No benefit
C. W. R.	Generalized	Intradermal	30	0.05 cc. (1:5,000)-0.2 cc. (1:2,000)	90 per cent relief in one attack; none in subsequent attack following year
J. B. L.	Generalized	Intradermal	9	0.03-0.1 cc. (1:2,000)	No benefit
L. B.	Generalized	Intradermal	20	0.02 cc. (1:100,000)-0.2 cc. (1:2,000)	No benefit
		Intravenous	3	50-125 cc.	
S. H.	Generalized	Intravenous	8	50-100 cc.	No benefit
R. R.	Generalized	Intradermal	25	0.05 cc. (1:100,000)	25 per cent improved by intradermal injections, unaffected by intravenous injections
		Intravenous	3	50-100 cc.	

TABLE 3.—*Results of Histamine Therapy in Patients with Miscellaneous Diseases Thought to be Associated with Atopic State*

Patients	Diagnosis	Method of Administration	No. of Injections	Dose and Solution	Results
H. U.	Prurigo	Intradermal	6	0.02-0.15 cc. (1:2,000)	No benefit
J. M.	Prurigo	Intradermal	6	0.02-0.15 cc. (1:2,000)	No benefit
C. K.	Generalized pruritus	Intradermal	7	0.02-0.05 cc. (1:2,000)	Very slight relief; treatment discontinued
		Intravenous	2	50-100 cc.	
H. A. R.	Pruritus ani (probably allergic)	Intradermal	9	0.01-0.1 cc. (1:2,000)	No improvement

Since prurigo begins as a papular urticaria and has been often found in victims of definitely atopic diseases, there seemed to be some reason for hope that histamine might be of benefit. After six intradermal injections there was no evidence of any effect on the disease in either of the patients treated, and the treatment was discontinued.

One patient with generalized pruritus which was thought to be of allergic origin was treated with histamine by both the intradermal and the intravenous route, but only slight improvement was obtained.

One patient with pruritus ani associated with digestive trouble and with no recognizable local cause of the pruritus was treated with nine intradermal injections of histamine, without any effect.

SUMMARY

Twenty-six cases are recorded in which histamine treatment was given. The diseases in these cases included chronic urticaria and angioneurotic edema, atopic dermatitis, prurigo mitis, generalized pruritus and pruritus ani. The results of the intradermal, subcutaneous and intravenous administration of histamine are given.

CONCLUSIONS

From a study of my series of cases and of the available literature the following conclusions seem justifiable:

1. Treatment by injections of histamine solution—intradermally, subcutaneously or intravenously—is beneficial in a large proportion of patients with chronic urticaria and rapidly curative in some whose conditions have resisted other methods. The most promising plan would seem to be to give two to four daily intravenous injections followed for a week or two by intradermal or subcutaneous injections. Histamine should not be regarded as the solution to all troubles with chronic urticaria, and dietary restrictions, attention to focal infection and relief of nerve tension must still have their share of attention in order to obtain complete cure and freedom from recurrences.

2. In atopic dermatitis, histamine cannot be depended on for relief of the pruritus or for resolution of the dermatitis. An occasional patient is apparently benefited. When given intravenously the drug had no prompt action, such as was observed in some cases of urticaria, and those patients receiving benefit gave evidence of improvement only after a number of small doses were administered intradermally or subcutaneously. It is possible that further experience with different technics and different doses will show the way to greater effect of histamine treatment in atopic dermatitis.

3. Daily small doses seem more effective than larger doses given at longer intervals. An exception to the preference for small doses is the slow intravenous drip method, by means of which larger doses may be given.

4. No serious symptoms are likely to occur from the doses of histamine usually given intradermally. The intravenous administration

of histamine by the slow drip method is a safe procedure. Epinephrine should be available when the drug is given intravenously, although it is seldom needed.

5. In some cases of urticaria it has been noticed that intradermal injections afforded more relief than subcutaneous injections.

6. After prolonged treatment with histamine by the intradermal or subcutaneous route little change was noted in the cutaneous sensitivity to histamine, as shown by the wheal response to intradermal injection.

The histamine phosphate solutions used in this investigation were furnished by Don Baxter, Inc., Glendale, Calif.

931 First National Bank Building.

ABSTRACT OF DISCUSSION

DR. RICHARD S. WEISS, St. Louis: I should like to ask Dr. Smith the following questions: What criterion for judging cure was employed in these cases of urticaria? How long after treatment was stopped did relief last? How many months have gone by since the patients were last observed? Has the improvement or cure been permanent?

DR. LESLIE M. SMITH, El Paso, Texas: It is difficult to tell whether these patients are permanently benefited or cured, or not. The majority of the patients had chronic urticaria which had lasted a long time. In 1 or 2 the condition lasted about a month; in the others the condition was of several months' duration. In 1 it had lasted for ten years, almost continuously.

Most of this work has been recent, in the last year. I have been able to follow all of the patients for at least one to three months, and some of them for six months or more. As the symptoms had been more or less continuous before then and as long remissions have been obtained, I feel that something has been accomplished. Whether the condition will recur in some of the patients or not I do not know. Dr. Alexander reported some recurrences after some of his spectacular results with the intravenous administration of histamine, but response to a little more treatment, and apparently, according to his statements, the patients became well after that and remained so.

LOCALIZED AMYLOIDOSIS OF THE SKIN

REPORT OF CASES; THE INTRACUTANEOUS CONGO RED TEST AS A DIAGNOSTIC AID

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AND
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JERUSALEM, PALESTINE

Lichen amyloidosus (Freudenthal[1]), or amyloidosis localis cutis nodularis et disseminata (Gutmann[2]), has become, since its description by these two authors, a well known clinical entity. The cause of the disease, however, is still unknown, and we think that every contribution to the knowledge of its clinical and pathologic features is of importance.

Koenigstein,[3] in an interesting chapter on cutaneous amyloidosis, discussed all related problems known at the time and mentioned all authors working in this field. He divided amyloidosis of the skin into two principal classifications: (1) universal cutaneous amyloidosis and (2) localized forms. The localized forms, with which we are concerned in this paper, are further subdivided, with the following modifications: (1) similar to lichen simplex chronicus (Vidal), (2) with deviations from the Vidal form, (3) similar to lichen planus, (4) appearing as prurigo and (5) not similar to any known disease.

During the last decade some new reports have appeared, and further progress has been made in this field.

Sannicandro[4] proposed a fundamental division of amyloid degeneration of the skin into four types: (1) generalized amyloidosis with participation of the skin (extremely rare), (2) atypical systemic musculocutaneous amyloidosis of Lubarsh (extremely rare), (3) primary cutaneous amyloidosus and (4) secondary cutaneous amyloidosis.

From the Dermatological Department of the Rothschild Hadassah-University Hospital.

1. (*a*) Freudenthal, W.: Amyloid in der Haut, Arch. f. Dermat. u. Syph. **162**: 40, 1930. (*b*) Dowling, G. B., and Freudenthal, W.: Lichen Amyloidosus, Proc. Roy. Soc. Med. **32**:1029, 1940.

2. Gutmann, G.: Amyloid of Skin: Two Cases, Nederl. tijdschr. v. geneesk. **2**:4480, 1928; Weiteres über Amyloid der Haut, Dermat. Ztschr. **53**:235, 1928.

3. Koenigstein, H., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 4, pt. 3.

4. Sannicandro, G.: La degenerazione amyloide della cute, Gior. ital. di dermat. e sif. **74**:1499, 1933.

Sannicandro [4] agreed with Gutmann that the third type represents true primary amyloidosis of the skin, and on the basis of 10 cases made the following deductions: A. This form appears more frequently in old age. B. Pruritus is constantly absent. C. The back is the main location. D. The clinical picture cannot always be compared with that of a known disease. E. The amyloid deposits are constantly in the papillary layer. F. Hyperkeratosis is not constant. He considered this isolated amyloidosis of the skin to be a degenerative phenomenon, no doubt in connection with the elastic tissue. Especially noteworthy seems to us the observation not stressed in previous reports that the main characteristics are an eruption of pigmented spots on the trunk and shagreen-like skin, in which amyloid nodules can be observed. Maschkilleisson [5] was able to demonstrate amyloid in areas remote from those clinically affected, and Freudenthal in areas nearly but apparently free from amyloid. A further contribution has been made by Wucherpfennig,[6] who in his case found, besides characteristic changes of the legs, nodules on the extremities, on the scrotum and in the sacral region in which amyloid could be demonstrated.

Progress in diagnosis was made by the modification of Bennhold's congo red test, this substance being injected intracutaneously. Reports on this method appeared in 1936 by Nomland [7] and by Marchionini and John.[8] Good results were obtained by this method in 2 cases of Nomland and in 1 case of Marchionini and John, while the intravenous administration of congo red usually fails in cases of primary amyloidosis of the skin.

In the following cases this test, together with the clinical aspect of the disease, will receive special consideration, and its field of application will be widened.

REPORT OF CASES

CASE 1.—*History.*—A 66 year old patient, born in Russia, lived for the last four years in Palestine. He came to the outpatient department because of tinea cruris. Cultures for fungi gave positive results. At the same time the patient complained of lesions on his legs, which he had had for the last thirty years and which appeared after an "eczema." The affected parts did not cause any discomfort except itching, and that only during a turkish bath. There was nothing of importance in the family history; no serious diseases in the past were reported.

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5. Maschkilleisson, L. N.: Amyloid of Skin, Venerol. i dermat. **7**:23, 1930; Ueber Amyloid der Haut, Acta dermat.-venereol. **11**:77, 1930.

6. Wucherpfennig: Zentralbl. f. Haut- u. Geschlechtskr. **44**:132, 1933.

7. Nomland, R.: Localized (Lichen) Amyloidosis of Skin: Report of Two Cases, with Vital Staining of Amyloid Nodules by Congo Red Injected Intracutaneously or Subcutaneously, Arch. Dermat. & Syph. **33**:85 (Jan.) 1936.

8. Marchionini, A., and John, F.: Ueber lichenoide und poikilodermieartige Haut- amyloidosis zugleich ein Beitrag zur praktischen Diagnostik des Hautamyloids am Lebenden, Arch. f. Dermat. u. Syph. **173**:545, 1936.

Clinical Examination.—The patient was of medium height and of moderate muscular development.

The lateral and medial parts of both legs were affected from the knees to the malleolar region (limits controlled with congo red). The color of the foci varied from red to a dirty gray-brown. They were disposed in parallel lines going from the upper posterior part to the lower internal part and had a "rosary-like disposition." The primary eruptions had a diameter of 1 to 3 mm., were flat but palpable over the level of the skin, polygonal, transparent and slightly glossy and in general resembled the keratosis verrucosa of Weidenfeld. Single nodules showed fine desquamation. In the center of the lesion the nodules were disposed in groups,

Fig. 1.—The rosary-like amyloid is made evident by the positive reaction to the congo red test.

close to each other but not confluent; in the periphery they were isolated and gradually faded into normal skin. Single nodules were scratched and covered by crusts. There were only a few foci over the tibia, while the calves were completely free. Tinea cruris was present. The rest of the body was normal. The lymphatic glands were not palpable.

Laboratory Studies.—The congo red test repeatedly elicited positive reactions on both legs; in the genital and scrotal regions, affected by tinea cruris, the reaction was negative. Internal examination did not reveal anything of importance.

Roentgenograms of the lungs were normal. The Mantoux test with a dilution of 1:50,000 elicited a negative reaction and with a dilution of 1:40,000 a slightly positive reaction. There was 60 per cent hemoglobin in the blood. A blood count showed 4,700,000 red cells and 9,000 white cells, with 64 per cent polymorphonuclear leukocytes, 1 per cent eosinophils, 32 per cent lymphocytes and 3 per cent monocytes. Chemical examination of the blood showed: urea, 41.5 mg. per hundred cubic centimeters; uric acid, 3.3 mg.; dextrose, 105 mg.; chlorides (sodium chloride), 602.4 mg.; total proteins, 6.72 Gm.; albumin, 4.31 Gm., and globulin, 2.41 Gm., with an albumin-globulin ratio of 1.8. The basal metabolic rate was +18 per cent. The Wassermann and Kahn reactions were negative.

Histologic Examination (Pathological Institute, Professor Franco).—A biopsy specimen was taken from the center of the lesion on the right leg. There were no

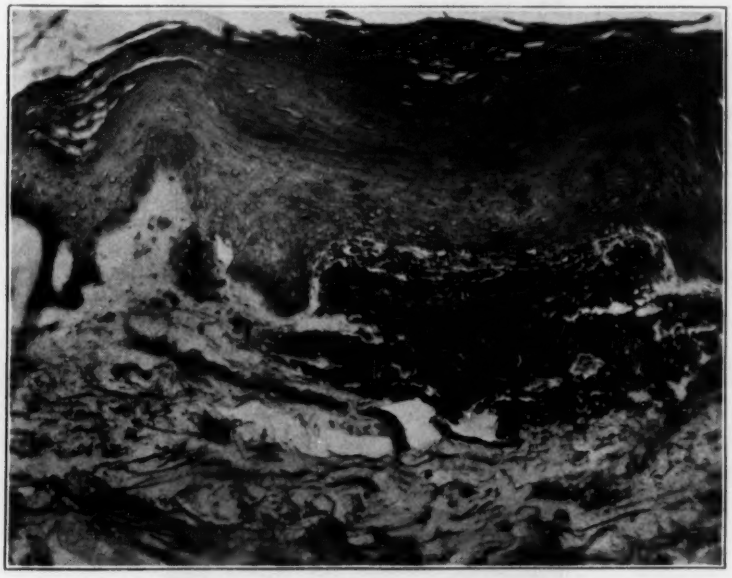

Fig. 2.—A large lump of amyloid directly under the epidermis (×900).

changes in the epithelium, except hyperkeratosis in some places. Directly under the epithelium there were disseminated small areas, separated from the normal tissue, whose appearance was considerably changed, the collagenous fibers being thick, in disorder, hyalinized and taking the acid dyes only imperfectly. Small thickened cells were found among these fibers. In the rest of the tissues the elastic tissue was normal; it was absent in the aforementioned small areas. Specific methods of staining showed that the condition present was amyloidosis; the remaining tissues showed no changes.

Treatment.—The treatment consisted of internal administration of potassium iodide and local application of ointments. Grenz rays were applied to the external part of the left leg. On Oct. 13, 1939 400 r (15 cm. focal skin distance, 15 milliamperes, 210 kilovolts, 0.01 mm. cellophane filter and a half value layer equivalent to 0.033 mm. of albumin) was given. There was no reaction. On December 13, 1,000 r was given with the same technic. There was slight erythema. On Jan. 5,

1940 1,000 r was given with the same technic. After two weeks a severe erythema appeared, which lasted for six weeks and left a moderate pigmentation. During the erythema there was severe pruritus. After the remission of the erythema the skin appeared to be softer and smoother in this region, owing to the disappearance of hyperkeratosis. The intracutaneous congo red test elicited a positive reaction. On March 31 another dose of 1,000 r was given. Further irradiation was given in doses up to those used in the treatment of specific granulation tissues, in order to study the influence of intensive irradiation on amyloidosis. On the right leg iontophoresis with potassium iodide, 2 to 10 per cent, was applied.

Summary.—In a 66 year old man with symmetric nodular keratosis of both legs, a positive reaction was elicited by an intracutaneous congo red test, and the diagnosis of amyloidosis cutis was histologically confirmed.

CASE 2.—*History.*—A 35 year old woman, born in Kurdistan, had lived for the past four years in Palestine. There was nothing of importance in the family history. No previous diseases were reported. For the last four years there had been severe pruritus of both legs.

Clinical Examination (Dec. 31, 1939).—The patient was of medium height and had good blood supply in the skin and mucous membranes, dark pigmentation of the skin and robust muscular development. There was pigmentation on both forearms, especially on the extensor surfaces, but also on the flexor aspects. Similar pigmentation partly in follicular disposition was present on the back, especially near the vertebrae, in the sacral region and on the loins. There were dark brown uniform pigmentation of the neck and scratch marks in the scapular regions. The pigmentation was dirty gray. A dirty gray to brown lesion, about the size of 2 palms, was seen on the right leg, especially on the lateral side, between the tuberositas tibiae and the malleolus lateralis. The lesion consisted of slightly elevated, not very transparent nodules, 1 to 3 mm. in size. The nodules were arranged in a mosaic-like form without evident stripes. The same picture was to be seen over the tibia, with interposed fresh and healing scratch marks. The medial parts of the legs were almost completely spared. The calves and dorsal parts of the feet were not affected. Similar lesions, in a slighter form, were to be found on the left leg. The focus began the width of a palm below the knee and ended closely over the mallelous lateralis, showing likewise a lateral disposition.

Laboratory Studies.—The intracutaneous congo red test elicited strongly positive reactions on both legs and negative reactions on the back and in the sacral region. Internal examination, including that of the lungs, showed no abnormalities. A blood count showed 3,940,000 red cells and 4,400 white cells, with 50 per cent polymorphonuclear leukocytes, 3 per cent eosinophils, 43 per cent lymphocytes and 4 per cent monocytes. The Mantoux test with a dilution of 1: 50,000 elicited a negative reaction. The Wassermann reaction was negative. Chemical examination of the blood showed no abnormalities. The basal metabolic rate was + 13 per cent Examination of the feces showed Trichuris dispar.

In order to study the affinity of the dye to the nodules, congo red was injected in the lateral side of the left leg, and this part was then irradiated with grenz rays in doses of 1,000 r, with the same technic as in the previous case. After forty-eight hours the reaction was not as clear as the control reactions; i. e., the tissue between the nodules was still intensively tinged with the dye. The reaction was clearly positive only after seventy-two to ninety-six hours.

Therapy.—Tincture of juniper tar was administered locally and potassium iodide internally.

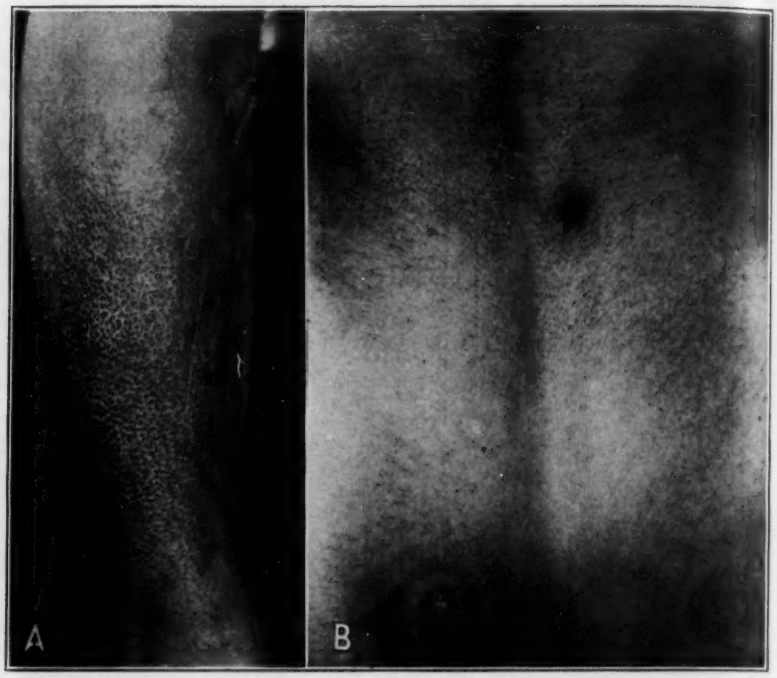

Fig. 3.—*A*, typical papules with mosaic-like disposition on the right leg. *B*, small areas of pigmentation on the back.

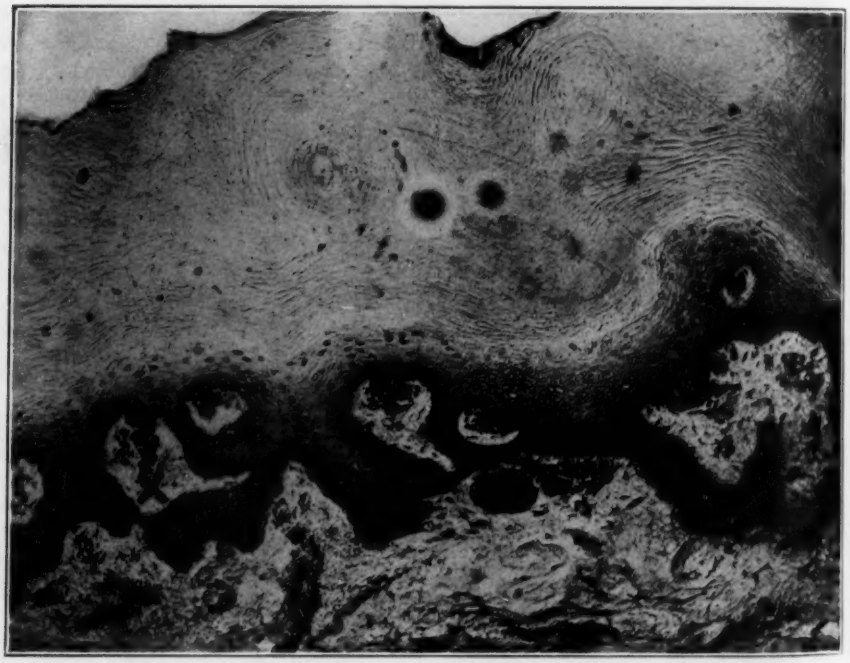

Fig. 4.—Small amyloid islets directly under the epidermis. *X* indicates islet in papillary body.

Course.—During one year's observation the aspect of the lesions changed slowly, especially on the right forearm and to a lesser degree also on the left forearm. The dotted pigmentation assumed the appearance of flat efflorescences, slightly elevated and barely palpable. The hyperkeratosis, present on the legs, was here almost completely absent. The pigmentation on the back seemed hardly changed since the first examination. The congo red test, repeated on March 19, elicited a clearly positive reaction on the forearm. On the back the reaction to this test was likewise positive, but here the electivity of the dye was less striking. In September 1940 pigmentation appeared on the arms; the intracutaneous congo red test elicited a positive reaction.

Histologic Examination (Pathological Institute, Professor Franco).—1. A specimen from the right leg, fixed in alcohol, showed numerous small foci of amyloidosis situated directly under the epithelium. There were several small cellular infiltrations in the skin.

2. In a specimen from an area on the right arm which showed pigmentation clinically there were numerous small foci of amyloidosis under the epidermis.

3. A specimen from the left loin showed the same changes as the specimen from the right arm.

Summary.—A 35 year old woman with cutaneous amyloidosis symmetrically disposed on the legs and progressing over the whole body, with severe pruritus, gave a positive reaction to a congo red test. Histologically amyloidosis was found.

Case 3.—*History.*—A 79 year old man, born in Russia, had lived for the last twenty-seven years in Palestine. There was nothing of importance in the family history. In 1929 he was admitted to the department of internal medicine of the Hadassah Hospital because of chronic bronchitis. For the last year he had complained of pruritus of the right leg.

Clinical Examination.—The patient was of medium height. There was senile atrophy of both legs, especially of the dorsum pedis. Cyanosis was present. There were dirty gray discoloration and lichenification of the skin of the right leg in the region between the tuberositas tibiae and the malleolus lateralis. The focus consisted of small nodules, 1 to 3 mm. in diameter, disposed densely and in groups in the center and dispersing toward the periphery. No confluence was to be seen. The efflorescences were clearly transparent, hard and glossy. The same process was present to a lesser degree in the tibial region, where numerous excoriations were seen.

The lateral part of the left leg showed slight desquamation and deeply situated small red efflorescences. The nodules were situated in a network of blood vessels visible through the skin, and the appearance of the lesions in this region was similar to that of poikiloderma. The efflorescences were barely palpable, not elevated and about 1 mm. in diameter. Changes of the skin facets in the perineum were observed.

Internal examination showed chronic bronchitis. Further thorough examination of the patient was impossible, as he failed to return to the clinic.

Laboratory Studies.—The intracutaneous congo red test elicited a clearly positive reaction on the lateral parts of both legs and a negative reaction on the perineum.

Half a year later the patient reappeared. The condition of the right leg was unchanged. All the efflorescences on the left leg had disappeared, but the evident venous design persisted. The congo red test showed, however, that the nodules which had apparently disappeared could be made visible by the dye.

Histologic Examination (Pathological Institute, Professor Franco).—1. A specimen from the right leg showed small foci of amyloidosis closely under the epidermis, which was atrophic (absence of the papillary relief). There were small cellular infiltrations of the skin, also in the proximity of the epithelium. The infiltrations were more or less distant from the amyloid foci. There were no changes of the vessels, glands, hair and muscles (arrectores pilorum).

2. A specimen from the left leg showed normal epidermis, small lymphocytic infiltrations around the vessels and normal elastic tissue. The stain for amyloid was negative.

Summary.—A 79 year old man had different clinical forms of amyloidosis on the legs, namely, the lichenoid form on the right leg and a form identical with that described by Freudenthal in Jadassohn's handbook on the left leg.

Fig. 5.—Left leg (*A*) before the congo red test and (*B*) forty-eight hours after the test.

Case 4.—*History.*—A 64 year old man, born in Lithuania, had been in Palestine for the past two years. There was nothing of importance in the family history. His parents died in old age. One son was living and well. During the last twelve years the patient had noticed an increase in the size of the abdomen and had complained of itching of both legs. The itching was sometimes very severe, while at other times it disappeared spontaneously. According to the patient, the foci on the legs were sometimes more clearly visible. No improvement followed roentgen ray treatment.

Clinical Examination.—The patient was of robust constitution, with a slightly flabby face, enlarged veins on the chest and a fat abdomen. Senile angiomas spread over the body, especially on the abdomen. Small areas of yellow to dark brown pigmentation were present in the inguinal region. Pigmented areas on the

back and in the lumbosacral region were somewhat rough. There were no abnormal changes on the arms. Scratch marks were present on the extensor surfaces of the forearms, and slight lichenification was seen on the upper third of the forearms. On the left forearm the surface of the skin was more elevated. Varices were present on the lower extremities.

On the right leg changes extended from 3 fingerbreadths below the patella to 3 cm. above the lateral malleolus (these borders were defined by the intracutaneous congo red test). The most distinct changes were on the lateral side of the leg, over the tibia and 2 fingerbreadths medial to it. On the lateral side was a plaque, the width of 4 fingers, with lichenification and mosaic-like structure. These lesions extended to the tibia, where there were two depigmented scars but

Fig. 6.—Large deposits of amyloid with infiltration of round cells.

no efflorescences. The upper part of the calf showed no lesion either macroscopically or with the congo red test. There was a single area of pigmentation on the distal third with a positive reaction to a congo red test. The primary efflorescences were partly square and partly polygonal, elevated, rough, compact and not clearly transparent. They were grouped in the center and discrete at the periphery. The whole lesion was keratotic and covered with small scales.

On the left leg the localization was also lateral, reaching the tibia, the medial parts being only slightly affected. There was a darkly pigmented lichenified focus above the malleolus lateralis, with a less pigmented scar in the center. From this focus a strip about 0.5 cm. wide, consisting of small nodules, extended toward the region of the caput fibulae, where it widened into a broad focus, similar to the distal one.

Laboratory Studies.—The intracutaneous congo red test elicited a positive reaction in the affected regions of both legs, the limits of these foci being

established exactly by means of this test. On the forearms and on the back the reaction to this test was negative. An intravenous congo red test showed normal excretion. The urine was normal. Examination of the feces showed Trichuris dispar. The blood count and the sedimentation rate of the blood were normal. The Wassermann and Kahn reactions were negative. Chemical examination of the blood showed no abnormalities except an increased cholesterol value, of 260 mg. per hundred cubic centimeters. The basal metabolic rate was — 7.5 per cent.

Histologic Examination (Professor Franco).—A specimen from the right leg showed that the epithelium was in some places slightly and in others decidedly hyperkeratotic. The intrapapillary foci gave a positive reaction for amyloid.

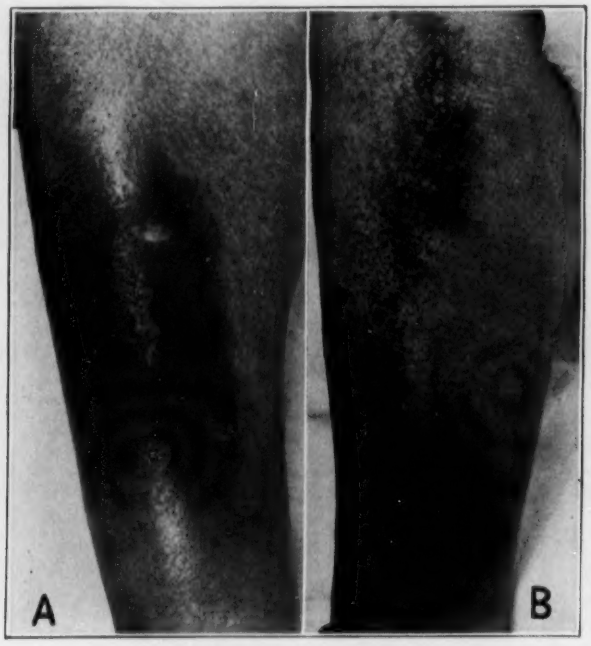

Fig. 7.—*A*, two depigmented scars, almost free from amyloid. *B*, typical amyloidosis above and area of pigmentation below.

Summary.—A 64 year old man had for twelve years, foci of lichen amyloidosus on the legs with a picture resembling lichen of Vidal. On the left leg were two foci widely separated but connected by a strip of pathologic elements. The congo red test elicited positive reactions, and amyloid was shown histologically.

Another case (case 5) shows that sometimes the existence of lichen amyloidosus can be neither accepted nor excluded with certainty. The congo red reaction was for a long time doubtful and then became slightly positive. The histologic examination also showed a mild amyloid reaction. Clinical deviations from the typical picture of the other cases are to be found; but the primary efflorescences in case 5 were clinicallv

exactly the same as in the cases already described, and so was the resistance to any kind of treatment.

CASE 5.—*History.*—A 25 year old man, born in Hungary, appeared on Oct. 31, 1937 for the first time in our outpatient department, stating that for the previous year he had noticed lesions on the extensor surface of the right forearm and on the thigh. There was nothing of importance in the family history. Except for having frequent attacks of angina he had always enjoyed good health.

Clinical Examination.—The patient was of the blond reddish type and of medium height. The blood supply of the skin and mucous membranes was satisfactory. The muscles and fat were well developed.

An 8 by 6 cm. plaque was present on the extensor side of the right forearm, beginning 2 fingerbreadths below the olecranon and covering the center of almost the whole forearm. The plaque was yellowish and consisted of single elements resembling blisters, but on palpation they appeared to be rough, hard elements. The nodules were yellow-brown, transparent, 1 to 3 mm. in size and in the center

Fig. 8.—Condition similar to the neurodermatitis on the left forearm. *X* indicates site of removal of tissue for biopsy.

densely aggregated but not confluent, and they extended in some places onto the flexor side. There was decided lichenification. The tops of the efflorescences were smooth, a few being covered with fine scales, which could be easily detached. After material was removed for biopsy, the typical efflorescences reappeared on the scar. A yellow-red lesion, 16 by 8 cm., was seen on the right thigh above the patella. Here the nodules were similar in form and disposition, and many were clearly follicular. On palpation, the whole lesion gave the impression of a file. There were scratch marks. The skin in general was well covered with hair but was bare in the region of the foci. In the center of the foci there was lichenification. The arm showed a naevus pigmentosus and the neck ephelides. Internally there were no pathologic findings.

Laboratory Studies.—The blood was normal. Examination of the urine and feces showed no abnormalities. There were no fungi. The Mantoux test with dilutions of 1:50,000 and 1:1,000 elicited negative reactions and with a dilution of 1:100 a positive reaction. The reactions to the congo red test were repeatedly doubtful and then became slightly positive. Chemical examination of the blood showed no abnormalities. The basal metabolic rate was + 15 per cent.

Histologic Examination (Professor Getzowa).—A specimen from the right forearm was fixed in dehydrated alcohol and 4 per cent solution of formaldehyde. The epidermis was thinned. There was slight hyperkeratosis. The papillary bodies were wide and domed shaped. In the subpapillary region there was an infiltration of small, round and fusiform cells, with the latter also invading the papillary bodies. Bands of infiltration penetrated the depth perivascularly. Congo red stained the fibers of the corium reddish (outside the layer of infiltration); the fibers were rather thick. When stained with methyl violet the fibers were slightly metachromatically bluish. Besides, there were numerous thin fibers (evidently elastic fiber) which were stained a deep blue. The anatomic diagnosis was chronic dermatitis, probably with deposits of amyloid.

Treatment.—The lesion was resistant to treatment. The patient was treated with compound ointment of sulfur N. F., Dreuw's ointment and irradiation with ultraviolet, with roentgen rays and with Bucky's rays, besides autohemotherapy (ten injections), milk (three injections), sodium hydrocarpate (seventeen injections), sodium bromide, tuberculin and solid carbon dioxide (nine applications). In spite of these treatments, the lesion remained unchanged for three years.

Summary.—A 25 year old patient had nonsymmetric lichen amyloidosus of the Vidal type. The congo red test elicited uncertain reactions. Histologically the condition was probably amyloidosis.

COMMENT

In the 5 cases of lichen amyloidosus herein described there are five different clinical pictures. In the first case the legs alone were affected, which is true of most cases. In the second case, besides involving the legs, the condition invaded the extensor regions of the arm and forearm, as well as the back. Although the disease spread over a large part of the body, the patient enjoyed good health. In the third case a combined form was present, since the left leg showed a picture totally different from that of the right leg. In Jadassohn's handbook, Freudenthal reported a case with a picture corresponding to that found on the left leg. About this case Freudenthal wrote: "Of special interest are the changes on the dorsa of the feet. An irregular red to bluish network is here seen enclosing small pale islands of slightly atrophic skin. Flat, slightly shining, hardly visible nodules are to be seen in the red bands, some of them showing a central depression." In our case the dorsal parts of the feet showed a similar picture, but no nodules were seen and the reaction to a congo red test was negative. On the left side of the left leg, however, which showed the same picture, nodules were seen and the intracutaneous congo red test elicited a clearly positive reaction. This picture on the left leg is especially emphasized, since its clinical appearance was entirely different from that of the common lichen amyloidosus, and were it at all possible to compare it to any other dermatosis it would be similar, in this respect, to poikiloderma atrophicans vasculare of Jacobi. Of particular interest in the fourth

case is the fact that the foci were not connected but were widely separated and were joined only by bands of nodules. Of interest also is the finding of a scar without nodules in the center of the focus over the tibia. In the fifth case there were isolated foci on the forearm and thigh with evident lichenification between the nodules, reminding one of lichen of Vidal.

In almost all the cases the lesions had a striking similarity to the keratosis verrucosa described by Weidenfeld. The suspicion arises as to whether this clinical entity established many years ago will not turn out to be a local amyloidosis of the skin. In 4 of the cases no severe illness could be demonstrated at the time and no history of chronic diseases of long duration was found. In 1 case, however, there was a history of a hepatic complaint, of which at the time no traces could be detected, even with tests of hepatic function, except for a high blood cholesterol level, of 260 mg. per hundred cubic centimeters. It is remarkable that while the amyloidosis of the internal organs as well as the general cutaneous amyloidosis is known to result from severe general diseases, no etiologic factor can generally be found in lichen amyloidosus. The suspicion is voiced, from many parts, that this amyloidosis is not the same as that found in severe diseases, although histologically and chemically no differences have yet been found.

During the observations, which lasted in our cases from one to three years, changes of different kinds were seen in the extension of the foci. At some periods an extension and in others a shrinking of the foci was noted. These changes might depend on the keratotic layer, as has been already observed by Koenigstein, who found a flattening of the nodules after an intercurrent disease (erysipelas), though no influence on the amyloid could be demonstrated. The same might apply to our observation of an apparent improvement after irradiation with grenz rays. These observations should be taken as a warning against false therapeutic conclusions.

Of interest is the fact that the amyloid disappears in scars, though in 1 of our cases a recurrence could be observed in a scar resulting from removal of tissue for biopsy.

We are unable to confirm the statement of Sannicandro that itching is not one of the symptoms of amyloidosis. Only in case 5 was the condition subjectively asymptomatic, whereas in the other 4 cases there was pruritus of different degrees. Two of the patients consulted us only because of pruritus.

Histologically, the position of the amyloid always appears in the same layers, corresponding to the affinity of the limiting membranes. This characteristic represents the main differential sign between localized and generalized amyloidosis, all layers of the skin being involved in

the latter. The lumps are rather uniform in the same case but differ considerably in different cases. In case 3 the presence of round cell infiltration in the amyloid was striking. It is possible that the excoriations and continuous rubbing give a sufficient explanation for this histologic picture.

Therapeutically, as in all cases reported in the literature, no effect was obtained. Grenz ray irradiation was tried because it permits a higher dosage than do roentgen rays. After about 4,000 r was given in three fourths of a year, the congo red reaction remained positive, although it was apparently slightly different. The doses will eventually be further increased.

Trials of iontophoresis with potassium iodide, 2 to 10 per cent, are not yet concluded.

CONGO RED TESTS

For diagnosis, besides the histologic examination, the Bennholt intravenous congo red test is generally employed. But this test, based on the demonstration of the elimination of congo red in the urine, gives negative results in cases of lichen amyloidosus. We therefore employed a 1 or 1.5 per cent solution of congo red for subcutaneous or intracutaneous injections, as already proposed by the aforementioned authors. Since this modification of the Bennholt test has not been used extensively in practice, we wish to describe the method briefly.

One-tenth cubic centimeter is injected intracutaneously in the affected region, and after twenty-four hours in cases of amyloidosis of the skin the pathologic nodules are strongly stained with the red dye and the interposed skin eventually appears slightly stained. Sometimes it is possible after twenty-four hours to see an imbibition of the nodules without any staining of the surrounding tissues. More frequently, however, the reaction is clearly positive only after forty-eight hours. A picture of lichen amyloidosis with a positive reaction is shown by the photograph in the first case. Repeated controls confirm the high specificity of this test.

This intracutaneous modification of Bennholt's congo red test has opened new channels: (1) the exact delimitation of the extension of the infection, (2) the finding of amyloid nodules in apparently unaffected parts and (3) the demonstration of the relation of pigmented areas in other parts of the body to this disease.

The delimitation of the lesion is determinted by intracutaneous injections of congo red a few centimeters from the periphery of the foci. It is then observed that in tissues outside the foci single small points take the dye. The interesting observation was made that small brown pigmented spots were seen in the proximity of the foci, these being similar to small pigmented nevi, a part of which have taken the dye, the other

parts remaining unstained. It may therefore be assumed that these spots present the same process which is not fully developed.

This assumption has been confirmed in case 2. In this case we were able to observe a further spread of the condition on the skin of a great part of the body, although in a completely different form than on the legs. On the upper extremities (extensor surfaces), as well as on the neck, the back and the loins, numerous pigmented spots were present, similar to freckles but dark gray-brown. In these regions, contrary to what was seen on the legs, the skin between the spots did not show any changes. The number of these spots seemed to increase in the course of one year's observation. The spots in the beginning gave negative reactions to congo red tests, but later positive reactions were obtained on the upper extremities and on the neck, apparently at the time when the spots seemed to be slightly elevated over the surface of the skin and a shagreen-like change of different degrees of the skin was seen. In the region of the loins the spots still gave a negative reaction. The biopsy specimens taken from the left arm (positive reaction to the congo red test) and from the loin (negative reaction) showed unmistakably the presence of lumps of amyloid near the limiting membranes, as in the other cases, but to a much less degree. It is not impossible that these efflorescences, not regularly stained by congo red and apparently showing a reaction for amyloid histologically, represent the forerunners of amyloid changes.

The opposite could be observed in case 3. While at the first examination a picture similar to poikiloderma could be seen on the left leg, after half a year no pathologic changes could be clinically detected on this leg. The congo red test, however, elicited a probable positive reaction (fig. 5). Small flat nodules were present, similar to the other amyloid foci but much less evident. Surprisingly, no amyloid could be demonstrated histologically in this spot, while it could be on the other leg (fig. 6). We must assume that these amyloid nodules, though able to absorb a congo red dye intracutaneously, were unable to take the common dyes into the dead tissues. Unfortunately, a second control biopsy could not be performed.

SUMMARY AND CONCLUSIONS

Five cases of circumscribed local amyloidosis of the skin are reported.

The clinical and histologic pictures varied in all cases in spite of the same pathogenic factors being involved.

Identity of this condition with keratosis verrucosa of Weidenfeld is suggested.

A progression of cutaneous amyloidosis to distant parts of the body was observed, not involving any disturbances in the patient's general condition.

The use of the intracutaneous congo red test for the exact delimitation of the pathologically changed tissues, as well as for the possible detection of primary efflorescences not yet clinically evident, is for the first time recommended.

The detection of amyloid in apparently normal skin is described.

By means of this test, the identification of pigmented spots on distant parts of the body as forerunners of lichen amyloidosus was made possible.

PUSTULAR PSORIASIS IN A NEGRESS

HARRY NIEMAN, M.D.
DAYTON, OHIO

Since the publication of papers by Barber [1] and Ingram [2] in 1930 and Wrong [3] in 1933, numerous cases of pustular psoriasis have been encountered and recognized.

Psoriasis vulgaris is uncommon in Negroes. Both Fox [4] and Hazen [5] observed large series of Negro patients with cutaneous diseases other than syphilis. They found that psoriasis vulgaris was present in less than 1 per cent of their cases. Lane and Crawford [6] in a statistical study of 231 cases of psoriasis included only 1 case of a Negro. In both of these recent surveys no mention is made of pustular psoriasis.

In the following case pustular psoriasis of the palms and soles of a Negress is associated with psoriasis vulgaris of the usual sites. It appears that no other similar case has been reported.

REPORT OF A CASE

A Negress aged 44 had had no eruption previous to April 1940, when she first noticed patches of thick, dry scales on the shins. Within a few days the thenar eminences of the palms became simultaneously involved in a reddish, slightly scaling eruption. A week later the inner aspects of both feet became affected.

In the family history the usual vagueness was encountered beyond the second generation, but it is of interest that one grandfather was said to be a white man.

The patient was referred by Dr. T. H. Winans, of Osborn, Ohio, on Aug. 21, 1940. She appeared to be well developed and well nourished. The general medical examination revealed nothing abnormal. The examination of the skin showed nummular, verrucous, reddish patches on the extensor surfaces of the

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Presented at a meeting of the Cincinnati Dermatological Society on Jan. 8, 1941.

1. Barber, H. W.: Acrodermatitis Continua Vel Perstans and Psoriasis Pustulosa, Brit. J. Dermat. **42**:500 (Nov.) 1930.
2. Ingram, J. T.: Acrodermatitis Perstans and Its Relation to Psoriasis, Brit. J. Dermat. **42**:489 (Nov.) 1930.
3. Wrong, N. M.: Pustular Psoriasis, Arch. Dermat. & Syph. **28**:682 (Nov.) 1933.
4. Fox, H.: Observations on Skin Diseases in the Negro, J. Cutan. Dis. **14**:87, 1908.
5. Hazen, H. H.: Syphilis and Skin Diseases in the American Negro: Personal Observations, Arch. Dermat. & Syph. **31**:316 (March) 1935.
6. Lane, C. G., and Crawford, G. M.: Psoriasis: A Statistical Study of Two Hundred and Thirty-One Cases, Arch. Dermat. & Syph. **35**:1051 (June) 1937.

lower parts of the thighs, the knees and the legs. These areas varied from 1.5 to 3 cm. in diameter and were covered with dry, micaceous scales.

Involving the entire thenar eminences, the adjacent parts of the palms and the medial aspect of both insteps (fig. 1) were reddish, scaly areas. Closer examination revealed minute white pustules and minute brownish crusts scattered throughout these areas. Both pustules and crusts were superficial and for the most part small and discrete. There were subjective sensations of heat, throbbing and actual pain, most pronounced on the soles and to a lesser extent on the

Fig. 1.—Lesions of pustular psoriasis in a Negress.

palms. There was no evidence of suppurative paronychia or involvement of the mucous membranes. All of the toe nails were dull, thickened and friable. The eruption manifested a tendency to exact bilateral symmetry.

The Kahn and the Kline reactions were both negative. No fungus was found on repeated direct examination of the scales and pustules mounted in 20 per cent potassium hydroxide solution. Cultural examination was not attempted. The following histologic report was made by Drs. Satenstein and Sachs: "In the center of the section is a large epidermic cavity, the base of which is formed by the basal cell margin and a few layers of prickle cells (fig. 2). At the edges of the cavity the epidermis is moderately acanthotic, involving both the rete pegs and the suprapapillary plates. The granular and horny layers are present and somewhat increased. There is very little edema present within the epidermis. In

the subepidermic region the vessels are dilated and there is a small round and wandering connective tissue cell infiltration. There is a moderate interstitial edema. The cavity is entirely filled with cellular elements composed mainly of polymorphonuclear leukocytes. Many of the latter are degenerated. The diagnosis is pustular psoriasis."

DIFFERENTIAL DIAGNOSIS

Barber [1] originally concluded that pustular psoriasis was entirely distinct from acrodermatitis perstans. More recently [7] he has recognized

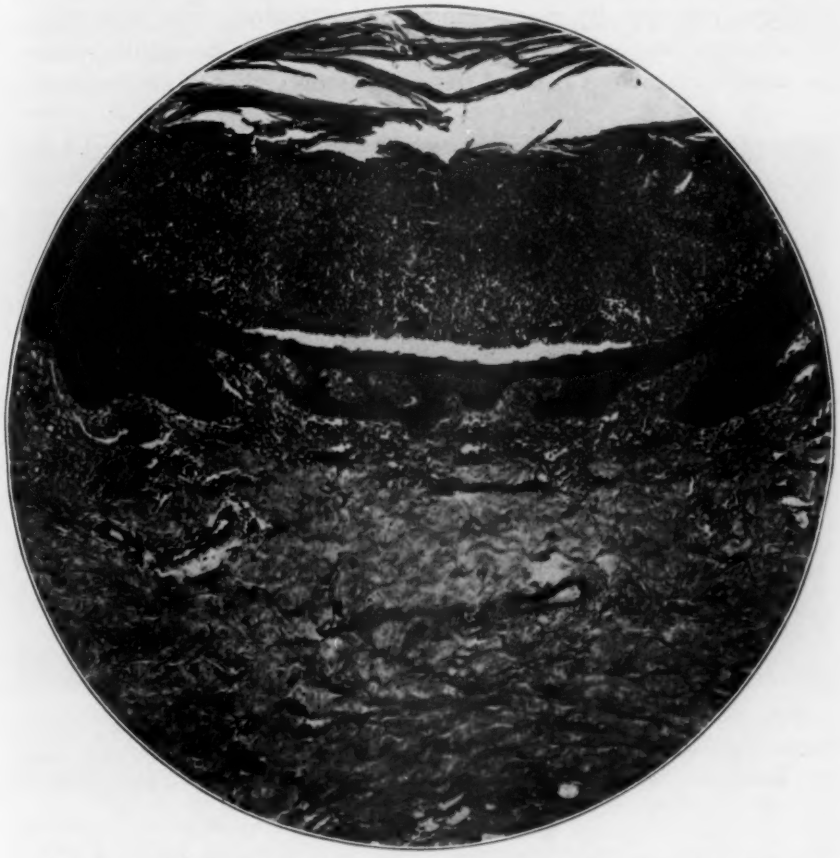

Fig. 2.—Photomicrograph of microabscess of pustular psoriasis, showing acanthosis, leukocytic infiltration beneath the microabscess and dilatation of the papillary blood vessels (× 50).

the pustular bacterid (Andrews [8]) as an entity and distinguished it from pustular psoriasis. The other probable diagnoses which must be considered in this case are dermatophytosis, dermatophytids, infectious

7. Andrews, G. C., in discussion on articles by Gross and Bloom, Arch. Dermat. & Syph. **38**:664 (Oct.) 1938.

8. Andrews, G. C.: Diseases of the Skin, Philadelphia, W. B. Saunders Company, 1938, p. 284.

eczematoid dermatitis and eczema. However, if one bears the following postulates of Barber [1] in mind, it is difficult to dismiss the diagnosis of pustular psoriasis: (*a*) the tendency to exact symmetry; (*b*) the sites of election, viz., the thenar eminences and the adjacent parts of the palm and wrist and the sole toward the inner side of the instep; (*c*) the formation of groups of intraepidermic pustules in reddened scaly patches and not as isolated lesions on previously normal skin; these pustules are for the most part small and discrete but sometimes become confluent, and they dry up to form brownish "scabs" in the horny layer; (*d*) the occurrence of acute exacerbations with congestion of the patches, the rapid formation of new patches, increased exfoliation and subjective

Fig. 3.—Higher power magnification of the section in figure 2, showing that the abscess is formed chiefly of polymorphonuclear leukocytes, with edema and leukocytic infiltration of the rete under the microabscess and acanthosis (× 144).

sensations of heat, throbbing or pain; (*e*) the absence of suppurative paronychia and of involvement of mucous membranes; the changes in the nails are the same as in psoriasis; (*f*) the negative results of microscopic examination for fungi, and (*g*) the association of this eruption with typical psoriasis elsewhere on the body.

SUMMARY

A case of pustular psoriasis of the palms and soles in a Negress, associated with psoriatic lesions on the usual sites, is recorded.

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Clinical Notes

DIFFERENTIAL DIAGNOSIS IN LEPROSY

HARRY L. ARNOLD JR., M.D., HONOLULU, TERRITORY OF HAWAII

When leprosy is considered in the differential diagnosis of cutaneous disease, it is all too frequently excluded on the basis of such statements as "examination of the nasal discharges failed to show lepra bacilli" or "the lesions were not anesthetic to light touch" or, worse still, "to pinprick."

It should be more widely realized that such observations as these do not exclude leprosy at all; indeed, they do not cast the slightest shadow of improbability on that diagnosis.

The principal diagnostic criteria for early leprosy are as follows: (1) almost any sort of cutaneous lesion—or, not infrequently, no lesion of the skin at all; (2) thermal anesthesia, frequently found in a cutaneous lesion but perhaps of even more significance when found in normal-looking skin (it is only occasionally associated with anesthesia to light touch and then usually in a small area roughly concentric with the thermally anesthetic zone); (3) muscular weakness or paralysis or even contractures (the latter only late in the course of the disease), most easily noted in the facial muscles by the presence of a widened palpebral fissure, lagophthalmos, a drooping oral commissure or the like; actual atrophy of muscle, and later contractures, in the interosseus and other muscles of the hands; (4) irregularly thickened subcutaneous nerve trunks, of which the ulnar and great auricular nerves are apt to be the most conspicuous, though others are often involved; (5) acid-fast bacilli—Mycobacterium leprae—in smears of tissue pulp obtained by inserting the corner of a safety razor blade 2 or 3 mm. into the skin (preferably over a lesion), rotating it 90 degrees about an axis perpendicular to the surface of the skin and withdrawing it, or in smears of tissue juice obtained by scraping the nasal septum with a submucous elevator or similar instrument, and (6) histologic changes—though I am sure few pathologists would care to make a positive diagnosis of any sort of leprosy (except the nodular variety, and preferably with acid-fast bacilli in the sections) on the basis of histologic changes alone.

The one point which above all the others may be relied on to exclude the diagnosis of leprosy with reasonable certainty is the absence of thermal anesthesia. Absence of thermal anesthesia is so rare an occurrence in leprosy that it is safe in practice to assume that it simply does not occur. This is by no means true of anesthesia to light touch (as with a camel's hair brush), which is often entirely absent in active leprosy; and it is even less true, if that were possible, of analgesia to pinprick, which is likely to be present only with moderately advanced conditions.

In searching for thermal dysesthesia, two ordinary laboratory test tubes filled with moderately hot (slightly less than painfully hot) water and chipped ice respectively will serve reasonably well. A more satisfactory device can be made by having a tinsmith braze a 1 inch (2.5 cm.) piece of ¼ inch (0.6 cm.) copper rod on the bottom of each of two fairly large (about 1 by 4 inches) metal centrifuge cups, which can then be filled with hot and iced water respectively

and corked. A folded paper towel wrapped about each cup and secured with cellulose tape will protect the examiner's hand from the heat of one and from the dew on the other and will also provide some insulation.

Failure to find acid-fast bacilli in proper preparations militates against a diagnosis of leprosy only in those cases of florid, acute "reacting" disease in which—if the disease in question is leprosy—a bacteremia and consequent flooding of the skin with organisms is undoubtedly present. Bacterioscopic examinations are useful when the results are positive but inconclusive when negative in leprosy as in other diseases.

If the diagnosis of leprosy is to be ruled out, then, let it be done on the basis of some such statements as the following:

1. Thermal anesthesia could not be demonstrated in the lesion(s) or elsewhere on the cutaneous surface.

2. There was no apparent weakness or paralysis of the facial musculature or atrophy or contracture of the small muscles of the hands.

3. The ulnar nerves were not thickened or nodular, and no other subcutaneous nerve trunks could be felt; or, if they could be felt, they did not feel nodular or irregularly thickened.

4. Cutaneous (or nasal or, better, both) "snips" and smears showed no acid-fast bacilli.

DERMATITIS DUE TO AN INGUINAL TRUSS

MILTON S. HARTMAN, M.D., BROOKLYN

While dermatitis from leather is not uncommon, the following case is of interest because of the wide dissemination of lesions beyond the point of contact, together with the extreme severity of the eruption.

REPORT OF A CASE

S. L., a man aged 60, was first seen on June 30, 1941. He had worn a bilateral inguinal truss for many years. About June 20 he found it necessary to replace his old, worn-out truss, which had never caused any irritation of the skin after years of use. About one week after constant use of the new support he noticed large blisters forming at the point of contact of the pads, but thinking these due to simple pressure, he placed dressings over them and continued to wear the support. When seen by me, he presented an intense erythema with overlying vesicles and bullae conforming to the shape of the truss. The skin under the pads was ulcerated. The dermatitis extended upward as far as the chest and downward to the ankles. The lower extremities were edematous, erythematous and covered with papules and vesicles. Pain and burning were so intense as to interfere with locomotion.

Patch tests with bits of leather from the truss elicited 4 plus reactions after six hours, the patient removing the patches.

The patient's brother had purchased an apparently identical support from the same dealer and had worn it for six to eight weeks without any discomfort or irritation of the skin. I gave the patient patch tests with leather from his brother's truss, and again 4 plus reactions were demonstrated after six to eight hours, denoting true hypersensitivity and not dermatitis from a primary irritant.

The patient's eruption cleared completely in two weeks after cessation of use of the new truss.

The manufacture of leather is an exceedingly complex process, many substances being involved. It is therefore difficult to determine the offending substance. No attempt was made in this case to discover this.

711 Bushwick Avenue.

PITYRIASIS ROSEA

Three Attacks in the Same Person

C. G. LaRocco, M.D., Cleveland

Granted that pityriasis rosea is a relatively common dermatosis and that instances are on record of two attacks, the occurrence of three episodes is sufficiently uncommon to merit recording. Engman and Kile [1] reported a similar experience, and Allen [2] made casual reference to six outbreaks in the same person.

REPORT OF A CASE

J. C. J., a white youth aged 17, was referred by his father, a physician. He was first seen with a typical pityriasis rosea in December 1940. His second attack was observed in March 1941 and his third in July 1941.

A tonsillectomy was performed when he was 5 years of age. He had mumps, varicella and pertussis at 6 to 7 years of age, ethmoiditis with abscess formation and surgical drainage at the age of 9 years and bilateral mastoiditis at 15, with recovery following administration of sulfanilamide.

Each attack of pityriasis rosea was ushered in by a typical herald patch on the right side of the back, but each time at a different level. The first eruption was papulosquamous and confluent to the degree of appearing almost solid from the neck to the knees. Subsequent episodes were similar in character but were much less extensive and severe. Each attack lasted from two to three weeks. The eruption disappeared completely in each instance after the second roentgen ray treatment with 75 r (unfiltered) of several areas. Constitutional symptoms were absent, and there was only slight pruritus. The Wassermann reaction of the blood was negative, and there was nothing unusual in the blood picture.

669 Rose Building.

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1. Engman, M. F., Jr., and Kile, R. L.: Three Definite Attacks of Pityriasis Rosea in the Same Person, Arch. Dermat. & Syph. **34**:272 (Sept.) 1936.

2. Allen, C. W.: Elephantiasis Arabum—Purpura Simplex—Pityriasis Rosea, Internat. Clin. **4**:340, 1897.

Correspondence

LARD VERSUS PETROLATUM IN OINTMENTS AND PASTES FOR DERMATOLOGIC USE

To the Editor:—In the eleventh revision of the United States Pharmacopoeia petrolatum was substituted for lard in official ointments and pastes. The twelfth revision is now being prepared. Experience in clinical practice during the past decade has indicated to many dermatologists that return to the use of lard is highly desirable.

Petrolatum, solid and liquid, lacks the property of emulsification leading to absorption of moisture from the surface of the skin. Cutaneous lesions accompanied by oozing or vesiculation thus tend to spread when covered with a petrolatum base. The animal fats, such as butter, lard and goose grease (benzoinated or not), have the property of emulsification. Their application to the skin leads to absorption of the ooze or product of ruptured vesicles. The physical and chemical properties of colloids and the intricacies of emulsion phases need not be discussed at this time. They are, of course, responsible for the therapeutic action of the animal fat.

It may be possible through the ARCHIVES to collect sufficient impressive data from clinicians and pharmacologists to convince the Committee on Revision of the United States Pharmacopoeia that it should reinstate the animal fat base for ointments and pastes designed for treatment of dermatologic conditions.

HERMAN GOODMAN, M.D.
C. P. WIMMER, M.A., PHAR.D.
New York.

ACANTHOSIS NIGRICANS OVERLYING METASTATIC MALIGNANT GROWTHS OF THE SKIN

To the Editor:—In the September issue of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY (**44**:349, 1941) Leslie Nicholas, describing an interesting case of acanthosis nigricans, stated: "In no instance heretofore, however, has it [acanthosis nigricans] been described in association with and immediately overlying deep metastatic malignant growths of the skin."

There is, however, a case reported by W. Dubreuilh (*Ann. de dermat. et syph.* **7**:67, 1918) in which metastases of a cancer of the stomach were found in the skin underlying acanthosis nigricans. This is the case of a 22 year old French soldier, who died about four months after onset of severe gastric symptoms and eight months after acanthosis nigricans made its first appearance. At autopsy generalized acanthosis nigricans, ulcerated carcinoma of the pyloric region and metastases in the deep skin or on the border of the hypoderm, in many lymph glands and in the lymph vessels of many internal organs were found. Cancerous injection of the lymph vessels without inflammatory reaction of the neighborhood had actually taken place in the skin and in other organs. The autopsy was not complete, as it was performed in a field hospital during the first World War.

Metastases in the skin along with other extensive metastases in internal organs seem to denote the highly malignant character of the primary tumor. This assumption is borne out by other qualities of the internal tumors associated with acanthosis nigricans, which I had occasion to review recently.

HELEN OLLENDORFF CURTH, M.D., New York.

SYPHILIS OF THE LARYNX

To the Editor:—I should like to comment on the article by Dr. Leon Felderman entitled "Syphilis of the Larynx: Report of an Atypical Case" (ARCH. DERMAT. & SYPH. **44**:667 [Oct.] 1941).

The history and observations in this case, even with the negative serologic reactions and the apparent improvement under bismuth therapy, might lead to a presumptive diagnosis of syphilis of the larynx but would not rule out a carcinoma, as it is well known that tertiary lesions of the mucous membranes, notably of the tongue, frequently become malignant.

It hardly seems likely that a competent histologist would have made a diagnosis of "squamous cell carcinoma, intermediate type III" without careful consideration and study of the cellular structure.

The absence of carcinoma at necropsy can be accounted for as the result of the epithelitis, necrosis and ulceration that frequently follow the roentgen and radium treatment of laryngeal cancer.

ERWIN P. ZEISLER, M.D., Chicago.

Obituaries

HENRY DARLING NILES, M.D.

1901–1941

The many friends and colleagues of Dr. Henry Darling Niles, of New York, were shocked and grieved to learn of his untimely death, on Aug. 27, 1941. He and his wife were instantly killed in an automobile accident in Montana, on the return trip of a motor tour to the west coast.

Dr. Niles was born in Brooklyn on Nov. 18, 1901. He was the son of the Reverend and Mrs. Edward Niles. His maternal grandfather, Henry Darling, D.D., LL.D., was the late president of Hamilton College.

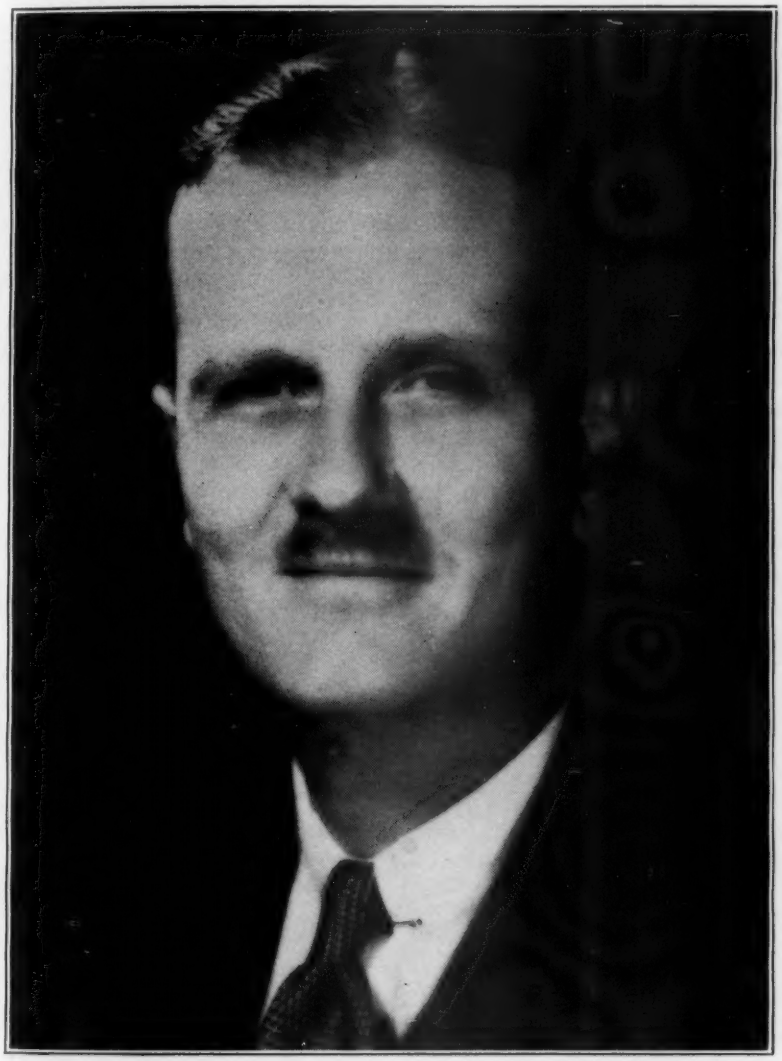
In 1917, at the age of 15, Dr. Niles participated in a competitive examination for entrance to Johns Hopkins University. He received the highest grade of all the candidates and was awarded a scholarship which provided him with two years' tuition at the University. In 1921 he received the degree of Bachelor of Arts and in 1925 the degree of Doctor of Medicine. While he was in medical school his academic record was extremely high. After serving an internship at the New York Hospital in 1927, he affiliated himself with the dermatologic departments of Cornell Medical School and the New York Post-Graduate Medical School and Hospital. From 1927 to 1931 he was an associate in the office of Dr. George Miller MacKee, where he received invaluable training. In 1931 he opened his own office in New York.

On June 30, 1928 Dr. Niles was married to Gertrude Catherine Edwards, of Cumberland, Ontario, Canada, the ceremony being performed by his father. Her loyalty and devotion to her husband and her unfailing interest in all of his professional activities contributed much to his enthusiasm for his work.

In 1940 Dr. Niles was appointed chief of one of the clinics of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital. In the same year he was also promoted from assistant attending dermatologist and syphilologist to attending dermatologist and syphilologist in the New York Post-Graduate Hospital. For fourteen years he was a member of the dermatologic staff of the Cornell Clinic and, after the opening of the Cornell Medical Center, of the New York Hospital outpatient department. In 1939 he was appointed assistant attending physician in dermatology to the New York Hospital. He was

also chief dermatologist and syphilologist to the West Side Hospital and Dispensary.

Dr. Niles greatly enjoyed teaching and was painstaking in the preparation of his lectures, which were always interesting. He held the posts



HENRY DARLING NILES, M.D.
1901-1941

of instructor and associate before being made assistant clinical professor of dermatology and syphilology in the New York Post-Graduate Medical School two months before his death. At Cornell Medical College he had been an instructor in dermatology for the past twelve years.

Dr. Niles was a diplomate of the American Board of Dermatology and Syphilology and was elected a member of the American Dermatological Association in 1939. He was also a fellow of the American Academy of Dermatology and Syphilology, the Americal Medical Association and the New York Academy of Medicine. He was a founder member of the Metropolitan Dermatological Society of New York and served as its president in 1936 and 1937.

Dr. Niles made many excellent contributions to the literature. He collaborated with Dr. G. M. MacKee in the last edition of his book "X-Rays and Radium in the Treatment of Diseases of the Skin" (ed. 3, Philadelphia, Lea & Febiger, 1938) and contributed the chapter "Diseases Due Wholly or Partly to Pyogenic Organisms."

Dr. Niles played a good game of tennis and enjoyed traveling, but his favorite "hobby" was dermatology. He often said that he derived his greatest pleasure from his work. His genial personality, gentleness, sincerity and integrity endeared him to his colleagues, students and patients and to his many personal friends. His passing is a distinct loss to dermatology.

THOMAS N. GRAHAM, M.D.

News and Comment

AMERICAN MEDICAL ASSOCIATION, SECTION ON DERMATOLOGY AND SYPHILOLOGY

Applications are now being received for places on the program of the Section on Dermatology and Syphilology of the American Medical Association for the meeting to be held at Atlantic City, N. J., June 8 to 12, 1942. All Fellows of the American Medical Association are eligible. Essayists who are not Fellows may be accepted by invitation. The program is usually assembled in the early part of December.

All applications should be addressed to Dr. Nelson Paul Anderson, Secretary of the Section on Dermatology and Syphilology, 2007 Wilshire Boulevard, Los Angeles.

DEATHS

Dr. Howard Morrow, of San Francisco, died from a heart attack on Oct. 22, 1941, at the age of 66.

CORRECTION

In the article by Dr. Leon Felderman entitled "Syphilis of the Larynx: Report of an Atypical Case" (ARCH. DERMAT. & SYPH. **44**:667 [Oct.] 1941), in the first sentence of the summary, on page 669, "typical syphilis" should read "atypical syphilis."

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

THE WATERHOUSE-FRIDERICHSEN SYNDROME: ACUTE BILATERAL SUPRARENAL HEMORRHAGE. JANVIER W. LINDSAY, E. CLARENCE RICE and LEROY ROBINS, Am. J. M. Sc. **201**:263 (Feb.) 1941.

The Waterhouse-Friderichsen syndrome is an acute and usually fatal disease of childhood. In a previously well but critically ill child without localizing signs this disease must be considered. The pharynx is injected, and the tonsils are hypertrophied and red. Cardiovascular collapse supervenes, and a stuporous condition becomes evident shortly after the appearance of the rash, which consists of petechial mottling of any part of the body, gradually extending over the body surface and leading to simulation of postmortem lividity. The symptoms are due to acute bilateral adrenal hemorrhage; the identity of the bacteriologic offender does not appear to be constant.

LYNCH, St. Paul.

SARCOIDOSIS OF THE EXTERNAL EAR. DAVID L. POE, Ann. Otol., Rhin. & Laryng. **49**:771 (Sept.) 1940.

Sarcoid of Boeck has been known for several decades and for long was thought to be a disease of the skin only. Today it is more fully recognized as a systemic ailment. Every organ of the body has been known to be affected, but little has been said about the ear. The cause of the disease is still unknown. The nodules are firm, nontender, noncaseating and of various sizes. Histologically the tissue resembles that of the small cell sarcoma. Many accept the disease as a type of tuberculosis, the cause of which is unknown. So far no satisfactory therapy has been found.

Poe reports a case of sarcoidosis in a Negress of 38 years, in whom the first symptoms apparently had been present twenty years before. When she was seen, the condition was general throughout the body. He describes the findings in some detail and expresses the belief that this is the first case in which involvement of the external ear has been described.

M. V. MILLER, Philadelphia. [ARCH. OTOLARYNG.]

LYMPHOGRANULOMA VENEREUM. W. HOWARD BARBER and WALLACE B. MURPHY, Ann. Surg. **113**:30 (Jan.) 1941.

The article deals largely with the surgical treatment of lymphogranuloma venereum. Radical surgical measures were employed in cases of obstruction and palliative surgical measures for the inflammatory but nonobstructive conditions. In 35 patients resections were made for anorectal obstruction, with a mortality rate of 14.3 per cent. The favorable convalescence of patients with uncomplicated conditions was remarkable.

WIEDER, Milwaukee.

THE ENDOCRINE DYSCRASIA OF ACNE VULGARIS IN WOMEN. CHARLES H. LAWRENCE and NICHOLAS T. WERTHESSEN, Endocrinology **27**:755 (Nov.) 1940.

Lawrence and Werthessen studied the urinary estrone equivalents and androgen values in 8 normal women and in 8 with acne. They report a significant decrease from the normal in the urinary excretion of estrogen by women with acne. No significant change in excretion of urinary androgenic material was observed. The increased ratio of androgenic material to estrogenic material was thought to be of greater significance than the quantitative decrease in excretion of estrogen. The

previous conflict between the report of Cornbleet and Barnes and that of Wile, Snow and Bradbury are reconciled by the authors after statistical analysis suggesting that it is invalid to conclude that either increased or decreased excretion of androgen occurs in association with acne.

STUDIES ON THE RELATIONSHIP OF SEX HORMONES TO INFECTION: IV. A STUDY OF THE DISPERSION OR CONCENTRATION OF INDIA INK IN SKIN BY CERTAIN SEX HORMONES. DOUGLAS H. SPRUNT and SARA MCDEARMAN, Endocrinology **27**:893 (Dec.) 1940.

Certain disease agents are aided and others are inhibited by the dispersion of disease incitant in the skin. The authors studied the dispersion of india ink because this is known to parallel the distribution of bacteria and viruses. They found that estrogens and pseudopregnancy significantly reduce this spread and that the castration of male or female rabbits reduces dispersion, but only temporarily.

LYNCH, St. Paul.

SUSCEPTIBILITY TO POISON IVY DERMATITIS. LOUIS ZISSERMAN, J. Allergy **11**:600 (Sept.) 1940.

In analyzing the records of 1,879 boy scout campers and their adult leaders who had a uniform opportunity to acquire poison ivy dermatitis, the author found that the degree of susceptibility was highest in boys from 12 to 16 years of age and diminished rapidly thereafter with age. The author found no correlation between sensitivity to poison ivy and such physical characteristics as weight and color of hair, nor was there correlation between sensitivity to sunlight and to poison ivy. The analysis also elicited that there was no correlation between susceptibility to poison ivy and the commoner allergic diseases, such as hay fever, asthma, eczema and hives.

QUANTITATIVE MEASUREMENT OF WHEALING IN HYPERSENSITIVENESS TO COLD TREATED WITH HISTAMINE AND HISTAMINASE. FRED E. MAISEL and HAROLD A. ABRAMSON, J. Allergy **12**:6 (Nov.) 1940.

The authors treated a patient with cold urticaria with graded doses of histamine and histaminase. Fifty milligrams of histamine and 525 units of histaminase were administered without any effect on the size of the wheal or on its rate of formation after the application of a standard cold stimulus.

The report includes a description of quantitative methods for studying the whealing response to cold.

ERYTHEMA NODOSUM FROM SULFANILAMIDE. ADOLPH B. LOVEMAN and FRANK SIMON, J. Allergy **12**:28 (Nov.) 1940.

The authors report a case of erythema nodosum from sulfanilamide. After its first appearance, the eruption was reproduced twice on further administration of the drug.

The histologic picture was indistinguishable from that of the classic type of erythema nodosum. Chemical tests of tissue taken from an active nodule showed no sulfanilamide.

Patch and intradermal tests with a saturated solution of sulfanilamide on both normal and previously involved areas gave negative results. Patch and intradermal tests with a tissue extract taken from an active nodule and with the blood serum taken at the time of the highest concentration of sulfanilamide in the blood gave negative results on both normal and previously sensitized areas.

FOOD SENSITIVITY AS A FACTOR IN THE ETIOLOGY OF ACNE VULGARIS. FRANK E. CORMIA, J. Allergy **12**:34 (Nov.) 1940.

In 25 of 80 private patients with acne vulgaris there was clinical evidence of food sensitivity. The report is based on a study of 32 patients, 12 of whom were

not affected by foods. The average age was 22 years, and the average duration of the disease five and seven-tenths years. A history of atopy was present in 10 families and a personal history of allergy in 4 instances.

Elimination of suspected foods greatly improved or cured 50 to 70 per cent of the patients with food sensitivity. Standard methods of treatment, including local application of astringents and roentgen ray therapy, were employed to combat collateral factors and to secure a complete cure.

The foods most commonly found by ingestion tests to cause clinical flare-ups were, in order of frequency, chocolate, tomatoes, nuts, spinach and wheat. The foods provoking the largest number of lesions were, in order, wheat, tomatoes, milk, chocolate, nuts and spinach.

The results of scratch and intradermal tests with foods were of little or no aid in the discovery of foods which caused clinical exacerbations.

DERMATITIS CAUSED BY CONTACT WITH COPPERWEED (OXYTENIA ACEROSA). L. SCHWARTZ and L. H. WARREN, J. Allergy **12**:63 (Nov.) 1940.

The authors report a case of acute dermatitis due to copperweed affecting both hands and wrists of a 55 year old white man, a plant chemist. The diagnosis was proved by the history and by patch tests. The authors found no previous reports in the literature of dermatitis from this plant.

The dermatitis-producing fraction of the plant is an alcohol-soluble, ether-insoluble substance.

The plant grows on arid, alkaline soils in the foothills and sagebrush plains of southwestern Colorado, Utah, Arizona and southeastern California.

MENDELSOHN, New York.

CONDITIONAL NEOPLASMS AND SUBTHRESHOLD NEOPLASTIC STATES. PEYTON ROUS and JOHN G. KIDD, J. Exper. Med. **73**:365 (March) 1941.

In this study Rous and Kidd have concerned themselves with the benign tumors which result from cutaneous application of chemical carcinogenic agents. Are they genuine tumors? The tar tumors of rabbits are tumors by all of the standard criteria except two: They have no capacity for independent growth, and the changes in their cells may conceivably be reversible.

The reported experimental studies indicate that tar warts which have apparently disappeared can be made to reappear after application of either carcinogenic or certain noncarcinogenic substances. Such ability to recur may persist at least six months.

The authors express the belief that this and other experimental evidence prove that the cells of the tar warts are irreversibly different from normal cells. Although the cells of tar warts may be unable to maintain themselves under ordinary circumstances, these cells persist in a subthreshold neoplastic state. Rous and Kidd say that the neoplastic state does not necessarily connote complete independence of behavior, and they conclude that the benign growths which tar elicits on rabbit skin must be classified as true tumors.

THE EXPERIMENTAL DISCLOSURE OF LATENT NEOPLASTIC CHANGES IN TARRED SKIN. IAN MACKENZIE and PEYTON ROUS, J. Exper. Med. **73**:391 (March) 1941.

MacKenzie and Rous tarred the skin of rabbits repeatedly for a period somewhat less than is ordinarily required to elicit growths and later subjected this skin to noncarcinogenic stimulation. In this manner they demonstrated that nonspecific stimulation may act as the deciding influence in tumor formation. Thus it becomes necessary to distinguish between forces that induce neoplastic cellular changes and those which determine the actual development of a tumor. This ability of tumor cells to lie latent and then to develop into growths after nonspecific stimulation is suggested as a possible explanation of clinical instances in which cancer appears after injury to apparently normal tissue. A carcinogenic

agent may have done its work years before and the cells it rendered neoplastic may remain within their morphologic context until an accident stirs them to proliferation. The medicolegal bearing of this report is obvious.

STUDIES ON THE SENSITIZATION OF ANIMALS WITH SIMPLE CHEMICAL COMPOUNDS: IX. SKIN SENSITIZATION INDUCED BY INJECTION OF CONJUGATES. K. LANDSTEINER and M. W. CHASE, J. Exper. Med. **73**:431 (March) 1941.

Sensitivity of the skin to simple antibodies has been characterized by the absence of demonstrable circulatory antibodies and the fact that hypersensitivity has been achieved mainly by application to the cutis. Landsteiner and Chase have previously demonstrated the possibility of obtaining a sensitizing effect of the skin by using the intraperitoneal route. In the present report they show that sensitivity of the contact dermatitis type can be produced with a material which is an antigen in the common sense and which ought to incite the formation of antibodies.

LYNCH, St. Paul.

CAT ITCH: CHEYLETIELLA AND NOTOEDRUS COMPARED. J. H. TWISTON DAVIES, Brit. J. Dermat. **53**:18 (Jan.) 1941.

Cat itch in human beings may be due either to Cheyletiella or to Notoedrus. Cheyletiella parasitivorax is not usually suspected because there is seldom anything obviously wrong with the cat, but examination will disclose on the anterior borders of the ears a grayish crust with a peculiar mosaic effect. To detect Cheyletiella parasitivorax infection, the cat has to be brushed out over white paper and the dust examined under a microscope. Apparently there may be natural immunity to Notoedrus. While there is no evidence of man to man infection with Cheyletiella parasitivorax, it seems that this can take place within twenty-four hours after exposure to Notoedrus. The clinical appearance of the two diseases is much the same. The primary lesion is a small urticarial papule which soon resembles a prurigo papule. There is a striking absence of secondary scratch lesions or infection. The eruption comes out in crops, and the distribution may be of the generalized or of the opportunist variety. Eruptions of Notoedrus itch are usually not generalized.

PHYSICAL PROPERTIES OF OINTMENT BASES. P. B. MUMFORD and R. M. MUMFORD, Brit. J. Dermat. **53**:45 (Feb.) 1941.

This article is apparently one of a series dealing with ointment bases and vehicles in an effort to bridge the gap between physical chemistry and therapy. "As much attention should be paid in prescribing to the terrain under treatment as has hitherto been devoted to the medicament incorporated in a vehicle—hitherto an unconsidered servant!" This article refers in greater part to the problem of physical interaction of vehicle and tissue. Subsequent articles will give consideration to therapeutic contents.

THE CARROT AS A CAUSE OF DERMATITIS. H. R. VICKERS, Brit. J. Dermat. **53**:52 (Feb.) 1941.

Seven cases are reported in which carrots produced dermatitis in susceptible persons. The eruptions were produced by contact with carrots in the course of work. The studies failed to ascertain the responsible constituent, but it was probably not the essential oil. Incidentally, routine cutaneous tests with carrots produced an incidence of 15 per cent of positive reactions.

THE SYNDROME OF EHLERS-DANLOS. H. STUART BARBER, JACK FIDDES and T. H. C. BENIANS, Brit. J. Dermat. **53**:97 (April) 1941.

This paper contains a report of 3 cases and a full review of the literature. The essential histologic features of the disease are: (1) the pars reticularis is

looser than normal and (2) the elastic tissue is in most cases increased and in coarser tangled bundles. Regarding the connective tissue pseudotumors, two main types occur: (1) that due to a swelling and bulging of the collagen bundles and (2) that due to connective tissue and giant cell proliferation.

CUTANEOUS BRIDGES AND FIBROMATOID FORMATIONS IN EXPERIMENTS ON ANIMALS. MARTIN FRIEDMANN, Brit. J. Dermat. **53**:113 (April) 1941.

The author sums up his findings as follows:

"1. The increase of the elastic fibres in fibromatoids is relative, resulting from withering of the rest of the connective tissue. The cause of this withering is not clear; the older the fibromatoids, the more extensive are the alterations.

"2. Put parenterally under the skin, the elastic fibers are not absorbed."

DERMATITIS CAUSED BY INSECTICIDAL PYRETHRUM FLOWERS (CHRYSANTHEMUM CINERARIIFOLIUM). J. T. MARTIN and K. H. C. HESTER, Brit. J. Dermat. **53**:127 (May) 1941.

A study was undertaken to ascertain the causal agent of the dermatitis, for if the active agent is something other than a pyrethrum its removal from extracts might be feasible, permitting the preparation of insecticidal products devoid of dermatitis-producing properties.

"The causal agent, or agents, of the dermatitis appears to be concentrated in the lower parts of the flower-head. Powdered flowers moistened with water gave a more intense reaction than the air-dried ground flowers. Pollen separated from the flowers gave only a slight reaction. . . . A colourless extract, obtained by petroleum ether extraction of the flowers mixed with charcoal, gave an intense reaction. The pyrethrins, tested in a concentrate containing 93 per cent of apparent pyrethrins as determined by a modified Seil method, are shown to be devoid of dermatitis-producing properties. The volatile oil, obtained by steam distillation of powdered flowers, is shown to be highly active. The oil after the extraction of a volatile acid fraction with alkali gave a less intense reaction, while the steam-distilled flowers also gave a positive reaction. The possibility that crystalline constituents of the petroleum ether extract of the flowers are contributory causal agents of the dermatitis is indicated."

"PRURIGO ANNULARIS." J. H. TWISTON DAVIES, Brit. J. Dermat. **53**:143 (May) 1941.

Two cases are described of an eruption in which "an expanding ring of the periphery" consisted of an ill defined band, 1 to 2 inches wide, "of minute urticarial or acuminate papules, 25 or so to the square inch, the more central of which had had their tops scratched off. This enclosed a uniformly pigmented refractory area. . . . The papules are similar to the small prurigo papules of scabies and pediculosis. . . . The eruption tends to appear or to be aggravated during pregnancy, but the latter is not necessary for its maintenance." In 1 case the patches disappeared after a course of autohemotherapy combined with the local application of dihydroxyanthranol.

RATTNER, Chicago.

SULPHANILAMIDE IN THE TREATMENT OF CLIMATIC BUBO AND SIMILAR CONDITIONS. FRANK HAWKING, J. Trop. Med. **43**:271 (Dec. 2) 1940.

Four patients with climatic bubo (lymphogranuloma venereum) were treated with sulfanilamide or sulfone (4, 4'diaminodiphenylsulfone glucoside), but no evidence was obtained that recovery occurred more quickly than in untreated patients. This treatment of patients with chancroid, or with ulcers resembling granuloma venereum, appeared to be more successful.

CONCERNING RIBOFLAVIN. ALFRED CLARK, J. Trop. Med. **44**:15 (Feb. 1) 1941.

Clark discusses lesions of the mucous membrane of the mouth to which Sebrell attached the name "cheilosis" and which the latter considered due to a deficiency of riboflavin. Sebrell's photographs and descriptions corresponded accurately to those of patients with pellagra in west Africa who used cassava as a principal item in the diet. Similar lesions were encountered by Clark in Ceylon. Clark agrees with Sebrell concerning the cause in these cases but states the belief that there are other factors besides deficiency of riboflavin, since in west Africa such cases are common even though cassava is remarkably rich in riboflavin. From his studies Clark expresses the opinion that in certain foods, including cassava, there is a chemical which inhibits the activity of riboflavn, probably a strongly inhibitory cyanic substance, mandelic nitrile.

AUTOPSY OBSERVATIONS IN A CASE OF MYCOSIS FUNGOIDES. L. M. PAUTRIER, G. HOERNER and F. WORINGER, Bull. Soc. franç. de dermat. et syph. **47**:8 (Feb.) 1940.

A patient with mycosis fungoides died of cachexia and ulcerative endocarditis. On autopsy characteristic granulomas of mycosis fungoides (not tumors) were found in the lymphopoietic organs, kidneys, myocardium, blood vessels, meninges and liver.

TRICHOPHYTIC CHEILITIS. B. BATCHVAROV and STOÏANOV, Bull. Soc. franç. de dermat. et syph. **47**:15 (Feb.) 1940.

In Bulgaria Trichophyton violaceum is the most frequent cause of chronic mycotic dermatitis in adults. The authors discuss a case of involvement of the lower lip in a man aged 28. Only 2 similar cases were found in the literature; rarely cases have been described in which trichophytosis has occurred on the buccal and vaginal mucosa. In their patient the hands, nails, nose, cheeks and lower lip were affected. The lip was erythematous and covered by gray scales from which T. violaceum was cultured. Treatment with iodine and compound ointment of benzoic acid N. F. resulted in rapid cure.

ERYTHEMA MULTIFORME DUE TO HORMONAL IMBALANCE (DERMATITIS SYMMETRICA DYSMENORRHOEICA). GEORGES GARNIER, Bull. Soc. franç. de dermat. et syph. **47**:71 (Feb.) 1940.

The author mentions that endocrine principles play a role in certain dermatoses, especially in the female. He describes the case of a woman aged 26 in whom erythema multiforme repeatedly developed at the time of the menstrual period. For three months after her periods she was given desoxycorticosterone acetate (progesterone), and at the time of the report her eruption had not appeared for four months. Garnier thinks that dermatitis symmetrica dysmenorrhoeica (Kreibich, Matzenauer and Polland) should be identified with erythema multiforme.

"INDURATIO PENIS PLASTICA" IN A PATIENT WITH RECTAL STRICTURE. JOSÉ MAY and B. V. FUENTES, Bull. Soc. franç. de dermat. et syph. **47**:81 (Feb.) 1940.

In other articles May has expressed the opinion that one of the etiologic factors in induratio penis plastica is the virus of lymphogranuloma venereum. He and Fuentes report the case of a man aged 59 who had induratio penis plastica in association with rectal stricture. The reaction to a Frei test was positive. There was definite improvement in the penile sclerosis following intravenous injections of Frei antigen. The authors mention that induratio penis plastica is also associated with Dupuytren's contracture and that Vignales has found positive reactions to Frei tests in patients having such contractures. They state the belief that certain sclerotic connective tissue processes may be caused by the virus of lymphogranuloma venereum.

LAYMON, Minneapolis.

Society Transactions

LOS ANGELES DERMATOLOGICAL SOCIETY

H. C. L. Lindsay, M.D., *Chairman*

Saul S. Robinson, M.D., *Secretary*

Jan. 14, 1941

A Case for Diagnosis (Ichthyosis?). Presented by Dr. Paul D. Foster.

N. W., a girl aged 4 years, presents a scaly erythematous eruption that first appeared on the hands and feet eight months ago and then spread to adjacent areas on the arms and legs. The involved areas appear to be exfoliating. The examination of the blood showed: hemoglobin, 74 per cent; erythrocytes, 4,100,000; color index, 0.9; leukocytes, 6,900; polymorphonuclear leukocytes, 35 per cent; lymphocytes, 65 per cent, and blood sugar, 80 mg. per hundred cubic centimeters. The urine was normal. The treatment has consisted of the administration of vitamin A, 75,000 U. S. P. units daily.

DISCUSSION

Dr. Irving Bancroft: I thought that the eruption was a type of ichthyosis with a superimposed dermatitis.

Dr. Julius Scholtz: I suggest a diagnosis of psoriasis with a possible superimposed dermatitis. I have observed several interesting cases in which the microscopic examination confirmed the clinical diagnosis of psoriasis. A precedent was set here when Dr. Fletcher Hall presented a case in which the histologic examination showed the typical picture of psoriasis. Since that time I have considered the condition in such cases to be psoriasis.

Dr. William Goeckerman: Careful study might make me change my opinion, but my diagnosis in this case is ichthyosis with a secondary dermatitis. The history, however, did not fit in with this diagnosis.

Dr. Samuel Ayres: I thought this condition might be a form of congenital ichthyosiform erythroderma.

Dr. Saul S. Robinson: My diagnosis is ichthyosis appearing first in early childhood. I suggest that a histologic examination be made for further study.

Dr. H. C. L. Lindsay: It appears to me as though this patient has ichthyosis. Patients suffering from ichthyosis are subject to inflammatory changes in the skin. Dr. Foster's treatment was for psoriasis, but the patient's eruption continued to get worse. If it is psoriasis, it should retain its characteristics. I have studied numerous cases of exfoliative dermatitis secondary to psoriasis. While the clinical characteristics were often entirely gone, the microscopic picture was still diagnostic.

Dr. Walter Schwartz: I favor a diagnosis of psoriasis. This case is very similar to that of an 8 year old boy who has been repeatedly presented before the Cleveland Dermatological Society (Arch. Dermat. & Syph. **38**:1013 [Dec.] 1938; **39**:170 [Jan.] 1939). The dermatologists of that society concluded finally that the condition was psoriasis. The microscopic examination showed psoriasis.

Angioma Serpiginosum. Presented by Dr. Saul S. Robinson.

Mrs. M. G., aged 56, has had an eruption on the lower extremities and trunk since July 1940. The lesions first appeared on the ankles in the form of "red dots" and enlarged to the size of 1 to 2 cm., with central clearing and annular

configuration. Some of the lesions are now telangiectatic and show slight central atrophy. There are no subjective symptoms. The Wassermann reaction of the blood was negative. The blood count and urine were normal. The histologic picture is compatible with a diagnosis of angioma serpiginosum.

A Case for Diagnosis (Schamberg's Progressive Pigmentary Dermatosis?). Presented by DR. SAMUEL AYRES JR.

Mrs. M. B., aged 67, was first examined on Nov. 26, 1940, because of an eruption involving the legs of one year's duration. The lesions first appeared during a period of hot weather and have gradually spread. At the time of the first visit the eruption involved all aspects of the legs and thighs from the ankles to the waistline and consisted of ill defined areas of brownish pink, with a suggestion of tiny hemorrhagic points. In spots the lesions were scaly and slightly thickened.

DISCUSSION

DR. SAMUEL AYRES: I am not in a good position to discuss these 2 cases because my mind is confused in regard to this condition. I have a feeling that these 2 patients probably have the same condition, or at least that the two conditions are closely related. I have never been satisfied as to how to classify such lesions. I have felt that they might represent some kind of a toxic disturbance in association with a mild vascular stasis. The lesions appear to start as small petechial areas that are slightly erythematous and scaly. Slight pruritus occurs in some cases. The lesions begin on the ankles and extend up the legs to about the waistline. Sometimes the spots appear on the arms. The involved areas usually disappear and leave some pigmentation. At times patches fade out and new ones appear intermittently. In Dr. Robinson's patient it appeared that there might be a small amount of atrophy. Personally, I am not satisfied with the diagnosis of Schamberg's disease. I think that this whole group of cutaneous lesions deserves a little more attention and discussion than it has had. Similar cases have been passed off with vague diagnoses.

DR. BEN A. NEWMAN: I did not place these 2 cases in the same category. I thought the condition in Dr. Ayres's cases was one of the group looked on as a stasis dermatitis with or without pigmentation. Dr. Robinson's patient presented an eruption seen in so many middle-aged patients as indefinite erythematous patches occurring on the thighs and trunk that have adherent scales. The disease appears gradually and spreads with or without treatment. I think that the punctate spots that Dr. Robinson pointed out are incidental. I could see no atrophy. These particular hemorrhagic puncta were also due to stasis. This condition is a type of dermatitis that I am unable to classify and name. Some dermatologists have called it eczema. I cannot possibly place it in the category of angioma.

DR. WILLIAM GOECKERMAN: I have a special working basis in cases like these that I evolved over years of observation. Dr. Ayres has touched on my conception. I believe that Schamberg's disease, angioma serpiginosum and purpura annularis telangiectodes (Majocchi's disease) represent merely a terminology covering certain reasonably definite morphologic cutaneous pictures. They represent varying degrees of injury resulting from an internal toxin with a special predilection for the capillaries. That a toxic agent will produce varying cutaneous pictures is well known. I need only call attention to tar, oil or carbon melanoses, which may cover the entire field from a simple dermatitis to atrophic changes which have been dignified by the term poikiloderma of Civatte.

DR. SAUL S. ROBINSON: I agree with Dr. Goeckerman that this type of cutaneous condition is due to a toxin. I had the good fortune of being able to study carefully the development of the lesions in my case from the onset. The cutaneous changes began in August, and I first examined the patient in early

September. During that early period, the lesions consisted of small puncta in the form of discrete macules and annular configurations. The eruption first appeared on the ankles and within a few days or one week's time spread up the legs and thighs and reached the level of the waistline. At the start the lesions were typical of angioma serpiginosum. A few months later I noticed slight atrophy and scaling appear within the lesions. These findings were of considerable interest. A few months ago the involved areas on the legs were bright red. Now they are fainter. Undoubtedly the lesions are clearing. Whether or not the improvement shown is related to the therapy used is unknown. Calcium gluconate was administered intramuscularly, and antipruritic shake lotions were prescribed for local application. The patient had a civil service position connected with the election board and was working long hours. There may be a connection of the cutaneous disease with so-called nervous exhaustion. Since the patient has stopped working and rested the lesions have greatly improved. The histologic examination showed a perivascular round cell infiltration in the upper part of the cutis with dilatation of the capillaries. The finding of dilated vessels microscopically accounts for the telangiectatic lesions seen on clinical examination. The microscopic picture in this case definitely rules out Schamberg's disease. There is no question but that there is an internal toxic cause associated with this type of cutaneous lesion. It may be that the final picture presented by the cutaneous lesions will fit in with what is known as poikiloderma.

Keratosis Blennorrhagica. Presented by DR. CLEMENT E. COUNTER.

Miss M. F., aged 19, has had thick, dry, hard palms and soles associated with a draining Bartholin abscess since July 1940. About one month after the onset a rough, fine, brown eruption appeared on the trunk and on the extremities. At the time of the first examination in October 1940, thick callus-like lesions were found on the feet, hands and elbows. Numerous keratotic plugs are now present on the palms and soles. The vaginal and labial examination shows no abnormalities. The Wassermann reaction was negative in July 1940. In December 1940 and January 1941 the Wassermann reaction was strongly positive.

DISCUSSION

DR. A. K. JENSEN: When I first looked at the lesions, I thought that the patient had psoriasis.

DR. FLETCHER HALL: At the time I saw this patient I did not know of the presence of a gonorrheal infection. I considered the eruption to be psoriasis. The nails showed typical pitting, and there was also the typical separation of the nail from the skin along the lateral margins of the nail. I consider the lesions on the elbows and knees to be papular psoriasis. The lesions on the sole looked entirely like psoriasis.

DR. SAUL S. ROBINSON: My diagnosis is pustular psoriasis. If this is true, I believe that a very interesting problem is brought up concerning the explanation of so-called pustular psoriasis. Bacterids may cause similar lesions. The terms pustular bacterid or pustular psoriasis have been used with confusion.

DR. CLEMENT COUNTER: I should like to mention some additional facts about this patient. She said that the cutaneous lesions appeared immediately after having a Bartholin abscess drained. At the time of her first visit, she not only had palmar and plantar lesions but also lesions which were generally distributed over her thighs and trunk. This generalized eruption was composed of follicular keratoses which were in groups about 3 cm. in diameter. These lesions disappeared spontaneously during the seven weeks after her first visit. It was not until the second visit that a specimen of blood was taken for serologic examination and the Wassermann reaction was found to be positive. She has had no treatment for syphilis. Arsenic could therefore play no part in the causation of the keratotic lesions.

Progressive Pigmented Nevus. Presented by DR. SAMUEL AYRES JR. and DR. N. P. ANDERSON.

Twelve years ago J. O., a Japanese aged *22*, noticed an eruption about the size of a silver dollar beneath the left clavicle. The lesion gradually enlarged to its present size.

Examination discloses a large quadrilateral macular area on the entire upper part of the left side of the chest presenting a scaly, diffuse, brownish, pigmented appearance. The histologic examination disclosed an irregular acanthotic epidermis with pigment in the basal cell layer. No nevus cells were present.

DISCUSSION

DR. FLETCHER HALL: There is one suggestion that I should like to make regarding treatment of this nevus, in view of an article by Oliver, Schwartz and Warren on occupational leukoderma (ARCH. DERMAT. & SYPH. **42**:993 [Dec.] 1940). I suggest that agerite alba (monobenzyl ether of hydroquinone), the rubber antioxidant found to be responsible for the leukoderma, be applied in a strength of 20 per cent in alcohol, ether and collodion.

A Case for Diagnosis (Mycotic Infection? Contact Eczema?). Presented by DR. A. K. JENSEN.

J. E. H., a barber aged *32*, states that the eruption on his hands began twelve years ago after he began cutting hair. Numerous patch tests with contacts have been made, and the patient was found to be slightly sensitive to karaya gum. He has used numerous salves and lotions and also received ten to twelve injections of Biscoff's dermatomycol. About one year ago twelve roentgen ray treatments, 75 r each, were administered to the hands. There is a deep-seated vesicular eruption on the fingers of both hands and on the palms. Some desquamation and fissuring are present. On examination the blood and urine were normal. The oidiomycin test gave a strongly positive reaction. The reaction to a trichophytin test was negative.

DISCUSSION

DR. M. J. WOLFF: I suggest that this patient be given patch tests with the various toilet lotions used in his occupation. Most of those lotions contain some quinine. Perhaps he is sensitive to one of them with which he comes in contact. Each time he has been away from work his hands have improved.

DR. SAUL S. ROBINSON: The patient told me that the solution used in giving permanent waves seemed to make his eruption worse.

DR. IRVING BANCROFT: Conditions like this are important but puzzling. Unfortunately, when a person becomes sensitive to an irritant, polysensitivity develops later.

DR. WILLIAM GOECKERMAN: The discussions on the differential diagnosis of dermatitis of the hands is, in my opinion, totally inadequate. I should like to call attention to an article by Wise and Wolff entitled "Dermatophytosis and Dermatophytids with Particular Reference to Differential Diagnosis of Dyshidrosiform Eruptions of Hands and Feet" (ARCH. DERMAT. & SYPH. **34**: 1-14 [July] 1936).

DR. H. C. L. LINDSAY: The sharp line of demarcation of this scaling plaque strongly suggests a fungous infection. When scales are easily removed, they should be examined under the microscope. It is advisable to culture some scales on Sabouraud's culture medium. Fungi such as that causing ringworm grow at ordinary room temperature, and a definite growth appears fairly early and may be luxurious by the tenth day. The treatment of a fungous infection on a workingman's hands should not interfere with the patient's occupation.

A Case for Diagnosis (Chronic Pityriasis Rosea?). Presented by DR. SAMUEL AYRES JR.

R. C., a man aged *36*, a teacher, was first seen on July 30, 1940, because of an eruption in the groin and axillas of about one month's duration. At the time

of the first visit the lesions were limited to the axillas and the upper medial aspect of each thigh. The eruption consisted of discrete and confluent, dime-sized to half-dollar–sized, irregular and circinate areas, with a crepe-paper-like surface and a central open collaret of scaling suggesting pityriasis rosea. The axillary hairs also presented a yellowish coating. The microscopic examination of scales from the groins and the axillas showed no fungi. Culture revealed only Staphylococcus. Microscopic examination of hairs from the axillas revealed the presence of leptothrix. The treatment has consisted of ultraviolet irradiation. The lesions completely disappeared after three to five applications but recurred in the same areas several weeks later.

DISCUSSION

DR. WILLIAM GOECKERMAN: I thought that the condition in this case was a mild dermatitis seen in any asteatotic skin as the result of application of banal irritants or of soap and water or rubbing of clothing.

DR. M. J. WOLFF: The spots disappeared and recurred on two occasions. The lesions were different from any that I had ever seen.

DR. SAUL S. ROBINSON: I examined a patient today with lesions similar to those in the presented case. The lesions were of three years' duration and were located in the axillas, on the abdomen and in the groins. Examination for fungi in my case gave negative results, and treatment with a sulfur and salicylic acid ointment had no effect on the appearance of the eruption. These lesions are characterized by their persistency. I should likewise classify this disease in the group of erythemas, possibly on an infectious basis. No treatment that I have been able to use in my case has been beneficial. I also considered in the differential diagnosis a possible persistent pityriasis rosea.

A Case for Diagnosis (Lichen Spinulosus? Keratosis Pilaris? Pityriasis Rubra Pilaris?). Presented by DR. N. P. ANDERSON.

Mr. R. G. M. has had a generalized eruption since the last week of December 1940. The ailment began with a swollen gland at the angle of the jaw on the right side of the neck. The swelling was tender and painful and was accompanied by general malaise. Two days later the patient noticed that the skin of his face felt lifeless or "dead." This was followed by tingling sensations in the face. Later he noticed that his face was swollen and tender. An intense sensitiveness of the hands and feet was also present. On questioning the patient relative to night blindness or other ocular symptoms, he at first disclaimed any change but later stated that his eyes were "tired" and burned.

Involving the entire trunk, arms and legs is a generalized, follicular, spiny, keratotic eruption, accompanied by definite swelling and scaling about the face and forehead. There is a diffuse scaling throughout the scalp with an underlying erythema. The palms and soles present a moderate thickening and hyperkeratosis. Thick layers of skin are desquamating from the palmar and plantar folds. The treatment consists in the application of theobroma oil to the affected areas and the oral administration of vitamin A, 25,000 U. S. P. units, three times daily.

DISCUSSION

DR. BEN A. NEWMAN: I believe, in the light of the knowledge gained during the past few years, that the so-called follicular keratoses are now considered a sign of vitamin A deficiency. Patients with these conditions are given massive doses of vitamin A. By massive doses I mean 50,000 or 75,000 U. S. P. units a day. Within thirty days after instituting this therapy the lesions disappear. Darier's disease also may disappear after the administration of vitamin A.

DR. SAUL S. ROBINSON: This patient stated in his history that he had an erythematous eruption for one week preceding the present eruption. There seems to be intense scaling on the palms and soles associated with an inflammatory condition of the throat or upper respiratory tract.

DR. WILLIAM GOECKERMAN: My diagnosis is an occupational dermatitis due to exposure to carbon during work.

Psoriasis Arthropathica Treated with Vitamin D. Presented by Dr. H. C. L. Lindsay.

A white woman aged 45, a school teacher, has had a generalized eruption since she was 5 years of age. The joints became involved when she was 23. The examination discloses a guttate type of psoriasis involving the scalp, legs, arms, abdomen and back. There are no lesions of the mucous membranes. The treatment has consisted of the oral administration of a vitamin D preparation in 25,000 U. S. P. unit doses, totaling 300,000 U. S. P. units a day. The lesions have shown improvement since she has been receiving this medication.

DISCUSSION

Dr. H. C. L. Lindsay: The reports on treatment of psoriasis with vitamin D vary in their evaluation of this medication. Ceder and Zon reported encouraging results in the treatment of psoriasis by ingestion of large doses of (crystalline) vitamin D (Wise, F., and Sulzberger, M. B.: Year Book of Dermatology & Syphilology, Chicago, The Year Book Publishers, Inc., 1937, p. 400). An article by Brunsting (Treatment of Psoriasis by Ingestion of Massive Doses of Vitamin "D," *Proc. Staff Meet., Mayo Clin.* **13**:280-283 [May 4] 1938) tends to confirm the observations of Ceder and Zon. A more recent article (Madden, J. F.: *J. A. M. A.* **115**:588-591 [Aug. 24] 1940) does not value the treatment so highly, although some good results were obtained in the treatment of arthritis. Notwithstanding the latter report, I gave this patient high doses of vitamin D, and her hands, which were previously seriously crippled, improved so that now she can write and carry on her work as a teacher. The psoriasis has improved slightly also. She had never been treated before with vitamin D.

PHILADELPHIA DERMATOLOGICAL SOCIETY

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Feb. 21, 1941

Scleroderma (Localized Type). Presented by Dr. Morris Markowitz and Dr. Sigmund S. Greenbaum.

K. B., a white man aged 62, presents moderately thickened atrophic macules and plaques distributed on the neck and chest, in the lumbosacral region and on the right lower extremity. There are no subjective symptoms. The eruption first appeared about a year and a half ago, coincident with repeated attacks of colitis with diarrhea. The Wassermann reaction of the blood was negative, and the blood count was normal. Routine chemical examination of the blood showed no abnormalities except a high cholesterol content, 395 mg. per hundred cubic centimeters. The patient was treated for pulmonary tuberculosis some years ago, with apparent complete arrest of the disease. Moderate improvement of the cutaneous lesions has been noted during the past six weeks following treatment with ammonium chloride, 0.5 Gm. given by mouth twice a day.

DISCUSSION

Dr. Fred D. Weidman: This case impresses me—and the history bears that out—as one in which the infiltration has been greater than it is at present. One has to palpate carefully to detect the fibrosis. I should say, though, that if the condition had improved materially, there would be no question about the diagnosis. The significant thing is that all of the improvement happened under the

influence of ammonium chloride. As the condition appears now, I first thought it was glossy skin, but after palpation, of course, it seems more than that.

DR. SIGMUND S. GREENBAUM: I have seen this patient three times at weekly intervals. There is a definite improvement in the sclerodermatous patches which he has on the entire trunk. Whether to ascribe this to the ammonium chloride or to the natural course of events is an open question. An important feature in this case is the concentration of calcium in the blood. Pautrier made the statement that in the vast majority of cases of scleroderma there is hypercalcemia, and this is not true in this patient.

DR. MORRIS MARKOWITZ: I believe that the increased cholesterol level in the blood serum is of significance. I do not think that it is ordinarily increased in scleroderma. A biopsy is indicated.

DR. C. C. THOMAS: The condition in this case impresses me as the type that sometimes responds favorably to prostigmine, and I think it would be worth while to administer this drug. I have administered 15 mg. of prostigmine bromide every hour and a half, from 8 a. m. to 8 p. m., provided there are no gastrointestinal reactions.

Results of Lumbar Sympathectomy in Sclerodactylia Following Raynaud's Disease. Presented by DR. SIGMUND S. GREENBAUM.

J. T., a white man aged 33, was well until six years ago, when he noticed his fingers and hands becoming progressively blanched. He later noticed that his feet and hands became white and cold in cold weather and that warming caused reddening and cyanosis. Three years ago the skin of all the extremities became thickened and a dark, purplish discoloration developed there and on the abdomen. Two years ago the patient began to complain of difficulty in moving the extremities and the diaphragm; there was also pain in the feet and hands. It was noted that minor cuts about the hands healed slowly. The perianal region became stiffened. The patient had had a tonsillectomy and an adenoidectomy. The blood pressure was 97 systolic and 63 diastolic. His temperature, pulse and respiration were normal. Electrocardiographic examination showed coronary insufficiency with myocardial damage. A roentgenogram of the hands showed loss of normal tufting of distal phalanges, destruction of the distal phalanx of the right index finger and osteoporosis.

DISCUSSION

DR. SIGMUND S. GREENBAUM: The patient states that both legs seem to be a little warmer; that would naturally follow the improvement of the vasoconstrictor effect by sympathectomy. This case is one in which Raynaud's disease precedes the sclerodactylia and shows what lumbar sympathectomy will do in some cases.

DR. DONALD M. PILLSBURY: I think, in view of the several reports of failure of sympathectomy to produce any permanent good effect, the possibility of parathyroidectomy should be considered.

Kaposi's Multiple Idiopathic Hemorrhagic Sarcoma. Presented by DR. HERMAN BEERMAN and DR. LOUISE TAVS (by invitation).

A. E., a white man aged 67, presents violaceous moderately firm nodules on both lower extremities, associated with pitting edema, especially on the left leg. There are hyperkeratotic lesions, especially on the soles. There is a purplish nodule on the left side of the palate. The patient noted nodules on his left foot four years ago which bled when traumatized. They increased in number, and a few of them also showed some tendency toward spontaneous regression. Elephantiasis, especially of the left leg, appeared subsequent to the onset of the disease. Pain is present in the posterior part of the right thigh and in the right heel. The right

leg was injured sixteen years ago in a stone quarry, the extent of injury being undetermined. Cystoscopic examination revealed no evidence of involvement of the bladder; prostatic enlargement was present. A gastrointestinal series of roentgenograms and roentgenographic examination after a barium enema showed no lesions. Roentgenograms of the chest and skull were normal. Roentgenographic examination of the spine revealed extensive arthritic changes in the lumbar portion of the spine and in the sacroiliac and hip joints. A blood count was normal. The blood urea nitrogen and the blood sugar were normal. An examination of the stool showed occult blood on Feb. 12, 1941 but not on February 18. The histologic picture of one specimen was not characteristic of Kaposi's sarcoma. Another biopsy specimen examined later suggested endothelioma. The patient was given roentgen ray therapy to the right leg, a total of 750 r at 120 kilovolts with a 2 mm. aluminum filter being given in three weeks, with marked improvement.

DISCUSSION

DR. FRED D. WEIDMAN: I think clinically the diagnosis is acceptable as rendered. The histologic picture is rather unusual, but I think that is due to the particular part of the skin that was excised. The histologic picture was more that of endothelioma. That is not surprising because there are parts of any Kaposi's lesion which will show morphologically more or less of an endothelial structure, so that would not stand in the way of the clinical diagnosis. There is no pigmentation in these sections, which shows that sometimes the picture is not histologically diagnostic, bringing up the old story of the selection of the appropriate leson for biopsy which will contain pigment and hemorrhage.

DR. SIGMUND S. GREENBAUM: One thing interesting in this case is the extension of the lesions along the lymphatic system, contrary to what one sees in sarcoma—extension through the blood system. That suggests epithelioma or carcinoma rather than sarcoma.

DR. DONALD M. PILLSBURY: In regard to treatment, I think the lesions will prove highly radiosensitive. Thus far, I have administered roentgen therapy to the right leg only, for purposes of comparison.

DR. FRED D. WEIDMAN: When a case of this kind is presented, one should always think of the condition as more than a cutaneous one. A number of cases have been reported in which there has been visceral involvement, particularly of the intestines, and I think it should be routine to inquire about the condition of the feces, particularly as to whether there may be any hemorrhage of the intestines, and tests for occult blood may be in order. When there are lesions of the intestinal mucosae, they are frequently so superficial that they will ulcerate, and this material may escape into the lumen of the intestine.

DR. EDWARD F. CORSON: My experience with the effect of roentgen rays in cases of this condition has been rather widely divergent. One patient some years ago responded in a satisfactory fashion, and for years there was no recurrence. Recently I treated a 15 year old youth in whom the tumors were expected to be radiosensitive, but the normal skin seemed much more sensitive than the tumors. In spite of the fact that he had a tremendous reaction to high voltage roentgen therapy, one could always see and feel the tumors in the area; and as soon as the roentgen ray reaction had subsided, the tumors would proceed in their growth. Eventually an attempt was made to remove them surgically, with fair results.

A Case for Diagnosis (Lichen Planus Atrophicus? Poikiloderma? A Condition Due to Bismuth and Arsenicals?). Presented by DR. DONALD M. PILLSBURY and DR. ROBERT C. LOFGREN (by invitation).

N. L., a white man aged 40, well developed and apparently healthy, presents a reticulated, hyperpigmented, slightly scaling, macular eruption of the whole

body with the exception of the hands, feet and inner aspects of the knees. The skin between the hyperpigmented macular lesions appears to be depigmented and associated with atrophy, telangiectasia and erythema. The sides of the forehead present hyperpigmentation and slight atrophy. There are remnants of previous reticulated white patches on the buccal mucosa of both cheeks adjacent to the angles of the mouth.

The patient was found to have a positive serologic reaction for syphilis while in a hospital for a hemorrhoidectomy in December 1939. Antisyphilitic treatment was begun. After thirteen injections of neoarsphenamine and after the twelfth injection of bismuth subsalicylate an eruption developed on the whole body. Treatment was stopped, but the eruption progressed and the patient was admitted to the hospital. He slowly improved. He was treated for blepharitis in June 1940 and for prostatitis two months later. He was first seen by the presenters on Jan. 9, 1941, for an evaluation of his eruption in relation to future antisyphilitic therapy.

The Wassermann reaction of the blood on Jan. 7, 1941 and on February 4 was positive. The urine on January 21 was normal. A complete blood count revealed 4,640,000 erythrocytes and 5,750 leukocytes, with 66 per cent polymorphonuclear leukocytes, 29 per cent lymphocytes, 2 per cent monocytes and 3 per cent eosinophils. An electrocardiogram and an orthodiagram were normal. Examination of the cerebrospinal fluid on January 14 showed no abnormality. In June 1940 a pathologist in another hospital had reported subacute dermatitis (medicamentosa) after examination of a biopsy specimen. On Jan. 8, 1941 Dr. Beerman, by exclusion, reported lichen planus. Spectrographic analysis of the skin by Dr. John W. Lentz showed 4 micrograms of bismuth per gram of pigmented skin and 2 micrograms per gram of nonpigmented skin. The quantity of arsenic found was insignificant.

The patient had been treated in other hospitals with sodium thiosulfate. He was given vitamin B complex by mouth, prostatic massage for prostatitis and yellow mercuric oxide 1 per cent for the blepharitis. On February 4 he was given bismuth and sodium tartrate, 0.1 cc., 0.2 and 0.5 cc. at weekly intervals, to test his tolerance. There was no flare-up in the dermatosis.

NOTE.—The erythema and the pigmentation have continued to fade.

DISCUSSION

DR. DAVID M. SIDLICK: In my opinion the diagnosis in this case, based on the clinical picture as well as on the history, is poikiloderma. The patient has a large liver, and his abdomen is prominent, owing, I assume, to the presence of ascites. This indicates an organic disease and perhaps explains the cause of the poikiloderma, since the latter condition is, of course, not an entity.

DR. THOMAS BUTTERWORTH, Reading, Pa.: I thought of poikiloderma. How was it ruled out?

DR. HERMAN BEERMAN: Dr. Pillsbury's mind was turned from that diagnosis by the possibility, shown histologically, that this condition might be, by exclusion, lichen planus. Dr. Weidman gave the differential diagnosis without knowing the history of the patient at all, and among the differential diagnoses was poikiloderma. This patient does have some annular-papular lesions, particularly around the neck.

DR. FRED D. WEIDMAN: I was doubtful from the histologic angle as to whether the condition was lichen planus or poikiloderma. After seeing the patient, my first impression was, as was Dr. Sidlick's, that the condition was poikiloderma. It would indeed be remarkably extensive and uniformly distributed for atrophic lichen planus. I did not see any structures which I thought were really telangiectatic; some accentuated pink markings intervened between the atrophic plaques, but they were different from telangiectases. I must confess that after this

brief clinical examination, I should not want to decide between the two diagnoses without further study.

DR. ALLEN D. KING, Wilmington, Del.: I was impressed with a certain amount of stippling or leukoplakial changes in the mucous membrane at the corners of the mouth and the rather diffuse red congestion of the throat. I think these changes would fit in with the diagnosis of lichen planus. I found none of them on the glans penis.

DR. DONALD M. PILLSBURY: We considered the diagnosis of poikiloderma. I realize that one should not let the histologic picture sway one too much. This man has an extensive pruritic eruption which developed during arsphenamine and bismuth therapy and is now subsiding. It is not progressing as one would expect if the disease were true poikiloderma. I think there is a little too much of a papular phase for poikiloderma, and there are lesions in the mouth which, while not diagnostic, are suggestive of lichen planus. I think the condition is in the end stage. There is nothing diagnostic of lichen planus, but I think that is the best possibility.

DR. SIGMUND S. GREENBAUM: I did not see any papules of lichen planus. It is difficult to explain the widespread telangiectasia on the trunk. Clinically the condition is poikiloderma vasculare atrophicans.

DR. DONALD M. PILLSBURY: I do not know that I can agree that there is true telangiectasia. Has Dr. Greenbaum ever seen a case of poikiloderma in which the condition appeared suddenly over a wide area?

DR. SIGMUND S. GREENBAUM: No, I have not. Did this man have an extensive inflammatory eruption?

DR. DONALD M. PILLSBURY: We did not see him while he had the original eruption, though according to a report it was very pruritic.

DR. SIGMUND S. GREENBAUM: The study of another section of those "red lines" might be of interest.

Purpura Annularis Telangiectodes (Majocchi's Disease). Presented by DR. J. P. GUEQUIERRE.

J. C., a white girl aged 5 years, tall, spare, of sallow complexion but not ill, presents on the medial side of the right arm from wrist to axilla and extending on to the pectoral area numerous irregularly placed areas in linear distribution

Purpura annularis telangiectodes.

of brownish pigmentation (hemosiderin) with punctate telangiectases. The lesions do not fade on pressure. Other newer lesions have appeared on the inner side of the right thigh, on the trunk and on the back of the scalp. The condition had its onset about ten months ago without apparent cause. There is no itching or crusting. There was pus in the urine in December 1940. Since the onset of the eruption the patient's hair has become darker, coarser and somewhat sparse.

Physical examination showed no abnormalities. The urine was normal. A blood count showed 4,740,000 erythrocytes; 11,500 leukocytes with 28 per cent polymorphonuclear leukocytes, 64 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils, and 272,000 platelets; there was 74 per cent hemoglobin.

The patient has been given calcium and vitamin D with no change.

DISCUSSION

DR. EDWARD F. CORSON: I should like to offer the diagnosis of Schamberg's disease. One is apt to think of progressive pigmentary dermatosis as occurring nearly always on the ankles, but cases have been reported of this condition on practically all parts of the body. While the light was not good enough to reveal the cayenne pepper lesions, I believe that the orange pigmentation suggests that condition more than the other diagnoses offered.

DR. J. P. GUEQUIERRE: Purpura annularis telangiectodes does occur on the arms and need not necessarily occur on the lower extremities. On examination in a good light the pigmentation is definitely suggestive of hemosiderin. To my mind, Schamberg's disease is totally different from this.

DR. FRED D. WEIDMAN: Of course every one has been struck by the fact that on the arm, at least, the lesion is linear. In the case of a child of this age one is tempted, of course, to think of a nevus. I suppose it is more on that account than any other that one might consider angioma serpiginosum or at least one of the formes frustes of angioma serpiginosum for the diagnosis, but I could not see any definite telangiectasia. There is pigmentation there, and I must admit that it is only owing to the age of the patient that I would venture to say anything at all in this direction. I do not like the concept of Schamberg's disease occurring on parts of the body other than the extremities. This case, I think, is one that must be followed.

NOTE.—The eruption cleared up in three months with only a few small areas of pigmentation remaining.

Metastatic Carcinoma (Scirrhous Type). Primary Lesion Undetermined.
Presented by DR. PATRICIA DRANT.

M. M., a white woman aged 65, presents generalized lymphadenopathy; the glands are hard, discrete and nontender. Subcutaneous nodules varying from ¼ to 1 inch (0.5 to 2.5 cm.) in diameter are scattered over the body. They are hard; some are freely movable, while others are adherent to the skin. The overlying skin is normal in color. Weakness developed in the right arm in July 1940, which became progressively worse and extended to the right leg by September 1940. This loss of power was not associated with pain or disturbance of tactile sensation. In the last two months she has had almost constant pain in the right side, in the lumbar region and in the flank, reaching to the anterior axillary line. There has been a loss of weight from 111 to 96½ pounds (50 to 44 Kg.) in seven months. The nodules have been present to the patient's knowledge for six months. A polypoid mass was removed from the cervix in January 1941, but the tissue was insufficient for microscopic diagnosis. The heart and mediastinum are shifted to the left side of the chest. The liver is enlarged and nodular. There is tenderness in the right lumbar region, and there is a suggestion of a mass in the right flank. Rectal examination was unsatisfactory. The examination of the stools gave negative results. Gastric analysis revealed achlorhydria together with much blood and mucus. No cancer cells were seen. The urine was normal. The Wassermann reaction of the blood was negative. A blood count was essentially normal. A roentgenogram of the chest showed atelectasis of the entire lower lobe and the posterior portion of the upper lobe of the left lung with a shift of

the mediastinum to the left. The roentgenogram showed no demonstrable lesion of the stomach or of the duodenum. There were no demonstrable lesions of the colon or of the rectum. Biopsy of a specimen of a subcutaneous nodule showed metastatic carcinoma with much dense fibrous tissue and small nests of packed carcinomatous cells, scirrhous in type.

DISCUSSION

DR. BERTRAM SHAFFER: About six months ago, at Mount Sinai Hospital, a patient died of carcinoma of the lung who some months before death had had an extensive nodular eruption involving the skin which was shown to be carcinomatous.

DR. PATRICIA DRANT: What type of carcinoma was it?

DR. BERTRAM SHAFFER: Bronchogenic.

A Case for Diagnosis. Presented by DR. J. P. GUEQUIERRE.

H. R., a white man aged 33, presents on the right side of the lower lip, between the angle of the mouth and the midline, a linear excavation with an oozing yellowish base. There is no induration. There are no enlarged glands. The patient has had frequent "cold sores" on the lip, which always cleared up rapidly. A year ago he consulted a radiologist when a "cold sore" did not heal in two weeks. He was given a total of 4,000 r in five treatments between March 14 and October 30, with no noticeable effect on the lesion. On Jan. 5, 1941 the area was electrodesiccated. The area involved was the same size as the present lesion. No noticeable healing has taken place. The patient has had a keratitis of the left eye, which was studied in the Wills Eye Hospital, but no diagnosis was ever made. The Wassermann reaction of the blood was negative. On March 18, 1935 at the Lankenau Hospital a diagnosis of interstitial keratitis of the left eye was made. Again the Wassermann reaction was negative. Examination of the cerebrospinal fluid showed a negative Meinicke reaction, 9 per cent lymphocytes, globulin (1 plus) and a colloidal gold curve of 01220000. No tuberculin test was made. Three courses of bismuth and neoarsphenamine were recommended. The patient had used "Clocreme" (a cod liver oil concentrate in a vanishing cream base) for three days previous to presentation.

DISCUSSION

DR. SIGMUND S. GREENBAUM: The lesion feels soft enough to exclude malignant disease. I think it is one of those chronic fissures of the lip that one occasionally sees, and the remedy, I believe, will be excision and the bringing of the edges of the wound together, if cure is to be obtained.

DR. THOMAS BUTTERWORTH, Reading, Pa.: I think that before excision is made it might be worth while to try splinting the lesion with collodion. I remember a boy with a deep fissure of the lip whom I treated with 5 per cent ichthammol in ether and collodion, with a good result.

DR. DONALD M. PILLSBURY: I suggest making a bacterial culture of material from this lesion, with the possibility of an anaerobic or symbiotic infection in mind. I agree with Dr. Greenbaum that there is a traumatic factor.

DR. A. STRAUSS: Was there an injury to the mouth in this case? I had a similar case recently in which the lesion developed after a fall.

DR. J. P. GUEQUIERRE: I presented this case largely as a protest against indiscriminate roentgen ray therapy. I wonder if the physician who gave the patient 4,000 r calculated his dosage incorrectly or whether his machine needs to be checked. I should expect to see more effect from 4,000 r, but it did not change the lesion at all, according to the patient's statement. The same physician electrodesiccated the lesion, and it looked no different after electrodesiccation. It does look a little better after application of a cod liver oil ointment for three days.

HERMAN BEERMAN, M.D., *Chairman*

DONALD M. PILLSBURY, M.D., *Secretary*

April 18, 1941

Dermatitis Medicamentosa (Bismuth). Presented by DR. EVAN B. HUME (by invitation).

V. P., a Negress aged 43, presents a generalized eruption, most evident on the trunk, back and inner sides of the thighs, consisting of raised and lichenified patches which are covered with white scales and have irregular edges. They vary in size from that of a dime to a square foot or more. The patient's breath is fetid, and the gums are inflamed and have a dark line. The eruption began two months ago as itching papules which coalesced. The itching is continuous. The patient had the usual childhood diseases, including scarlet fever. She has been under treatment for syphilis in another clinic for two months and has received intramuscular and intravenous injections. The urine was normal. The treatment for the cutaneous condition has consisted of local applications and sedatives by mouth.

DISCUSSION

DR. A. STRAUSS: If this condition is a bismuth eruption, it is the most extensive I have ever seen. I agree that it suggests some lichenoid eruption, but the history of onset and the presence of a bismuth line on the gums support the presenter's diagnosis.

DR. J. V. KLAUDER: The patient states that she has had more arsenic than bismuth. It is a question whether or not the condition is a lichen-planus-like eruption following the injection of arsenic.

DR. J. P. GUEQUIERRE: How many injections has she had? Has she been seen only recently, or was her skin observed prior to the development of the eruption? It occurred to me that possibly the patient had lichen planus which became worse after she received the injections.

DR. EVAN B. HUME (by invitation): The patient came in only yesterday, and I have had no opportunity to secure full data.

DR. BERNARD L. KAHN: Lichen planus may be aggravated by injections of bismuth or by local applications. I recently observed a case in which lichen planus was present on the forearm and tongue. After the application of silver nitrate to the tongue, extension of the lichen planus occurred.

DR. HERMAN BEERMAN: It might be worth while to have chemical studies for arsenic and bismuth made of this patient's skin.

Acrodermatitis Atrophicans Chronica. Presented by DR. ISADORE ZUGERMAN.

E. L., a white woman aged 39, presents redness and atrophy of the skin of the dorsa of the right hand, wrist and arm. The superficial blood vessels are visible. The skin is smooth and velvety and is easily lifted into folds which do not spring back into position. On the elbows and knuckles there are several firm, painless, fibrous nodules. On the arm the skin is edematous, slightly raised above the surface and erythematous, being dusky red. The patient first noted redness of the back of her right hand twenty-three years ago. She states that there has been no advance of the condition since 1936. Physical examination gives essentially negative results except for evidence of chronic gallbladder disease. During the past two months large doses of vitamin B complex and of vitamin C have been given.

DISCUSSION

DR. J. P. GUEQUIERRE: I have never seen acrodermatitis on one arm only. It usually occurs on both arms or both legs.

DR. A. STRAUSS: Some time ago I presented a woman with a process similar to that in this patient on one arm. My patient worked in an ice cream parlor for some years and had had the affected arm in salt water a great deal.

DR. THOMAS BUTTERWORTH, Reading, Pa.: I was surprised at the gouty-like character of the nodules on the elbows. They seemed stony hard, much harder than the usual nodules of this condition. It might be well to incise one of them to see if there is any calcification.

DR. SIGMUND S. GREENBAUM: This patient has three conditions: a diffuse atrophy over the dorsum of the right hand, an idiopathic macular atrophy as seen in the macular lesions on the left arm and the calcified deposits over the elbow and knuckles. It is difficult to conceive of one etiologic factor for all these. One thinks of an infectious or toxic agent or of some endocrine dysfunction.

DR. FRED D. WEIDMAN: The hernia-like projection of the skin at the margin of the process, under which there is a good deal of tumid material—it seems to be soft and fatty—makes me think of localized myxedema. If one considers the surface of the skin only, a diagnosis of poikiloderma atrophicans vasculare is justified. I think the consensus now is that this condition is not an entity, clinically or etiologically, but may be seen in a number of diseases, among which is dermatomyositis. I could not elicit a history of dermatomyositis. I think the condition might be called poikiloderma atrophicans vasculare in association with some condition of unknown cause.

DR. ISADORE ZUGERMAN: In a similar case of acrodermatitis atrophicans chronica Dr. E. B. LeWinn and I made fat tolerance tests, according to the method described in our article (*Am. J. M. Sc.* **201**:703, 1941). The blood cholesterol was within normal limits, but the curve obtained from results of several consecutive tests showed a percentage rise of 45 per cent less than the normal controls. One case is of no significance; however, it seems to show that the fat, in this case, is more rapidly withdrawn from the blood stream than in normal controls. There may be a relation between this abnormal behavior of fat and the loss of fat and atrophy of the skin in this type of disease.

Aleukemic Lymphoid Leukosis. Presented by DR. JOHN B. LUDY.

M. F., a white woman aged 71, noted a reddish pink area on the right side of her forehead in June 1937. The condition spread by addition of similar lesions to the right and below the original site. Slight itching and scaling were present. When presented before the Philadelphia Dermatological Society in September 1938 (ARCH. DERMAT. & SYPH. **39**:545 [March] 1939), the patient exhibited a patch of violaceous, rounded, moderately infiltrated papules and nodules with ill defined grouping. Many lesions were telangiectatic. The patient had typhoid at the age of 37, rheumatism at 19 and Bell's palsy sixteen years ago. She has a left-sided facial weakness. The Wassermann and Kahn reactions of the blood were negative. A blood count was normal except for 4 per cent large monocytes. Analysis of urine obtained when the patient was not fasting showed a specific gravity of 1.036 and 8.8 per cent sugar. Urinalysis during fasting showed a specific gravity of 1.041, 2.8 per cent sugar and a slight reaction for albumin. The blood sugar was 328 mg. per hundred cubic centimeters. The initial diagnosis was sarcoid, but Dr. Geschickter, of Johns Hopkins University, thought the condition might be aleukemic lymphoid leukosis of the skin, and a monocytic type was not excluded. There was no evidence of tuberculosis in the sections. The patient is presented now to show complete involution of the cutaneous lesions, probably indicating the correctness of the former diagnosis.

DISCUSSION

DR. FRED D. WEIDMAN: Aleukemic lymphoid leukosis is the diagnosis of the general pathologist in a case like this which concerns the difficult borderline cases of leukosis. I feel positive that the diagnosis here is Spiegler-Fendt sarcoid com-

plicated by diabetes. I thought so clinically, and I think the sections confirm it. Of course, such conditions are known to clear up, especially under arsenical therapy.

DR. E. F. CORSON: When this patient was presented before, there was no report of a urinalysis, and at this time she has definite diabetes. I think Spiegler-Fendt sarcoid is now generally considered to be one of the leukoses—not sarcoid.

Trichostasis Spinulosa. Presented by DR. DOUGLASS A. DECKER, Allentown, Pa.

M. W., a white man aged 21, presents on the shoulders, back and upper part of the arms hundreds of follicular, pinhead-sized papules, with a small lanugo hair in the center of each. The patient first noticed the eruption two years ago. When cleared in xylene and mounted in balsam, the hairs show typical trichostasis spinulosa. Salicylic acid ointment, 10 per cent, was applied locally but did not change the condition. However, it became much better in the summer, after exposure to the sun.

DISCUSSION

DR. E. F. CORSON: Grossly, this condition does not resemble typical trichostasis spinulosa. The follicular plugs that are usually present seem to be wanting. While the patient has folliculitis, I think it requires microscopic study to confirm the diagnosis.

DR. FRED D. WEIDMAN: Has this condition been radically improved by treatment? Have the spines been more conspicuous than they are now?

DR. DOUGLASS A. DECKER, Allentown, Pa.: That is the case. The patient worked on a farm for the summer and got a severe sunburn and tan. When he came to see me last fall on his return to school, he was practically cured. In the course of the winter the papules became evident again. I have frequently pulled out one of the hairs and demonstrated the typical plugs of trichostasis spinulosa. Whether the improvement was due to the sunburn or not I do not know.

DR. SIGMUND S. GREENBAUM: Because of the long duration of the condition and the absence of subjective symptoms, I offer the diagnosis of follicular seborrheic dermatitis, which in the presence of sunlight will often disappear. I think that the general term spinulism for these keratotic spines is a good one, as they are seen in a large number of follicular diseases and are not typical of any particular dermatosis.

DR. HERMAN BEERMAN: I think I can explain the disappearance of the trichostasis spinuosla without resort to sunlight. If one follows cases of this condition for a long time, one sees a cycle during which sometimes the lesions are present and at other times are not (Beerman, H., and Stokes, J. H.: Rosacea Complex and Demodex Folliculorum, ARCH. DERMAT. & SYPH. **29**:874 [June] 1934).

Dermatitis of Unknown Causation. Presented by DR. MAURICE BROWN.

H. C., a white man aged 42, presents a scarlet red band across the forehead with fine, almost imperceptible scaling. There are involvement of the upper part of the bearded area and slight seborrheic dermatitis of the scalp. Three years ago the condition began after the forehead was sunburned, and it has not changed since then. It oozes at times. Covering of the hatband has produced no improvement. The patient has been given six roentgen ray treatments recently, 75 r weekly, with improvement.

DISCUSSION

DR. A. STRAUSS: At first sight this patient's condition is rather typical of hatband dermatitis, but Dr. Brown says that he has taken precautions to eliminate that. The condition is of rather long duration. According to Dr. Brown, he has done everything that could be done, with no effects. I doubt that the precautions to eliminate the hatband as the causative factor have been complete.

DR. E. R. GROSS, Wilmington, Del.: I should like to suggest lupus erythematosus. I thought there was definite atrophy in the center of this lesion. There was a suggestion of telangiectasis, and the dermatosis has been present for three years.

DR. HERBERT J. SMITH: The condition looked like contact dermatitis to me.

DR. J. V. KLAUDER: I should consider a low grade cellulitis. There is inflammation, and the lesion is hot to the touch.

DR. DONALD M. PILLSBURY: The protective covering does not extend over the entire hatband. I feel, as Dr. Strauss does, that the hatband has not been eliminated as a factor.

A Case for Diagnosis (Roentgen Ray Ulcer? Epithelioma?). Presented by DR. J. M. SCHILDKRAUT, Trenton, N. J.

R. S., a white man aged 48, in 1933 had a small growth behind the left ear, which was removed. The lesion recurred and was removed again in 1934. The area did not heal and in July 1935 appeared as two separate rounded ulcers, about 1 cm. in diameter, with rolled waxy borders. It was treated with roentgen rays and healed after five erythema doses were given. In March 1936 two nodules appeared at the border of the previous site and were destroyed by electrodesiccation. In May 1937 a cluster of small nodules recurred on the posterior surface of the left ear and seemed to be attached to the underlying cartilage. Nineteen hundred roentgens of roentgen rays were given, and the area healed. In January 1940 an ulcer developed. The cartilage was exposed, and the area became suppurative. After several weeks it healed, with a dime-sized perforation through the external ear. In February 1941 the tissue around this perforation broke down, became red and painful and bled easily. The ulcer has extended, involving the greater part of the posterior surface of the ear. The patient has been treated with Aloe vera ointment, with some relief of pain.

DISCUSSION

DR. J. M. SCHILDKRAUT, Trenton, N. J.: The question in my mind is whether this lesion is an ulcer following therapy or an epithelioma. If it is cancer, it has been rather rapid in its spread. It took about ten weeks to reach its present extent. I have seen patients who have been given treatment for carcinoma of the tonsil and apparently cured who four or five years later began to have cyanotic patches in the skin at the angle of the jaw which broke down and would not heal, owing to fibrosis and cutting off of the circulation. This man had treatment with 1,500 r in 1935 and two years later 1,900 r. Whether that is sufficient to rule out the possibility of a slough in a radiosensitive person I do not know.

DR. J. V. KLAUDER: I thought this lesion was a basal cell carcinoma rather than radiodermatitis.

DR. I. ZUGERMAN: Dr. A. Strauss and I have had some success in the treatment of radiodermatitis with a hydrous wool fat emulsion.

DR. A. STRAUSS: I am of the same opinion as Dr. Klauder. I do not think that the lesion is a roentgen ray ulcer. I have seen several epitheliomas of cartilaginous structures that have broken down after becoming apparently well and have given rise to ulcerations of this type. According to some physicians with whom I have spoken, who have had great experience with this type of epithelioma, it is due to underdosage. Dr. Schildkraut's dosage, according to these physicians, would be a rather small one. I have had some little success with the emulsion to which Dr. Zugerman refers; ulcers heal rather well. It relieves the pain and the end results are fairly good. I give it to patients for application several times daily.

DR. FRED D. WEIDMAN: At the Oncologic Hospital amputation is recommended for conditions of this sort, and it is remarkable what a good artificial

ear can be made; plastic materials are used. It is fastened on a piece of wax to the bow of the spectacle. This man has a mutilated ear now, and I have an idea he would look better with a good plastic one.

DR. DONALD M. PILLSBURY: Dr. O. V. Batson, of the University of Pennsylvania, makes very presentable ears. I think this case is a good example of how difficult epitheliomas of the external ear or over the mastoid process are to cure. In many cases that I have encountered roentgen therapy is not particularly successful. I believe that as soon as the lesion is recognized, it should be widely excised, either surgically or by diathermy, and a plastic repair made, if necessary.

DR. THOMAS BUTTERWORTH, Reading, Pa.: It is my impression that in an early epithelioma over cartilage the results are better with heavily filtered radium therapy than with the low voltage roentgen rays that most dermatologists administer. Excise the epithelioma first, then apply the radium to the site.

DR. PATRICIA DRANT: I prefer to destroy epitheliomas developing over cartilaginous structures like the nose and ear by electrodesiccation rather than by roentgen rays or radium. Frequently severe, slowly healing and painful lesions follow the use of roentgen rays or radium.

NOTE.—The lesion later, on histologic examination, proved to be an epithelioma.

CHICAGO DERMATOLOGICAL SOCIETY

LEONARD F. WEBER, M.D., *President*

MICHAEL H. EBERT, M.D., *Secretary*

March 19, 1941

A Case for Diagnosis (Ulcer of the Penis. Tuberculosis?). Presented by DR. CLARK W. FINNERUD.

G. J. L., aged 42, was first seen on Jan. 20, 1941 because of a finger nail–sized indurated ulcer of the right side of the base of the penis of one week's duration. He thought it had begun as a pimple. There had been various exposures to infection through sexual intercourse. The lesion was without subjective symptoms.

After the first visit the lesion gradually increased in size, in spite of all treatment, until it had about the diameter of a silver quarter in the course of the following month, at the same time becoming considerably deeper. In the week before this presentation it has been healing steadily. At no time has there been any appreciable regional lymphadenopathy.

The patient had syphilis fifteen years ago, for which he received thorough treatment for several years. Since that time his blood has been checked at regular intervals, and the Wassermann and Kahn reactions have remained negative.

When the patient was first seen a dark field examination was performed and failed to show Spirochaeta pallida. The Wassermann reaction of the blood on that day was also negative. Eight or ten dark field examinations have been made since that time and as many Wassermann and Kahn tests have been performed, all of which have given negative results, the last within the past week. Several intracutaneous tests have been performed with Ducrey and Frei antigen, all of which have given negative results.

Histologic examination ruled out epithelioma and showed a chronic granuloma of tuberculoid structure. There was slight but definite caseation necrosis. On two occasions, once in consultation with Dr. Mitchell and once when smears were taken at the time the biopsy specimen was taken, Donovan bodies were thought to be identified. However, on further study I thought they were other than such bodies.

Locally, potassium permanganate soaks, ammoniated mercury ointment, roentgen rays and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) in powder and in ointment form have been used. The patient has also taken sulfanilamide by mouth in decreasing doses from 60 to 30 grains (4 to 2 Gm.) daily over a period of about two weeks. There has been some involution of the lesion since neoarsphenamine was first used intravenously on February 27.

DISCUSSION

DR. JAMES H. MITCHELL: I am in the dark as to the diagnosis. I made smears to look for possible inclusion bodies. I found some bodies which I sent to Dr. Finnerud as being suggestive, but they were probably nothing more than large streptococci.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: The sections showed all the features of inoculation tuberculosis together with caseation necrosis and definite tubercle formation. Clinically, however, one would expect to find some evidence of adjacent adenopathy, especially since the lesion has been present for two months. From the history the possibility of an inoculation tuberculosis seems likely, and I favor this diagnosis.

DR. OLIVER S. ORMSBY: Some time ago I saw a child with a lesion on the brow that resembled this one. It was an indolent, indurated ulcer. The lesion closely resembled a chancre. Several dark field examinations were made. When the condition had been present long enough for the Wassermann reaction to become positive if it were syphilis, a blood test was made, and the reaction was negative. During this time a gland beneath the jaw became enlarged. After several weeks small apple jelly nodules developed around the margin of the ulcer, and then the diagnosis of the primary complex of tuberculosis became evident. I think this patient presents the same condition.

DR. STEPHEN ROTHMAN (by invitation): The most helpful method for the early diagnosis of a primary tuberculous lesion of the skin is the examination of smears of material from the ulcer for tubercle bacilli. They are present in a large number of cases in the initial stage, at a time when the tuberculin reaction is still negative and the tuberculous structure has not yet developed.

DR. CLARK W. FINNERUD: I feel rather confident now, after listening to the discussers, that the condition in this case is inoculation tuberculosis. It seems that the histologic sections settle the diagnosis. Smears for acid-fast staining were not taken during the early stages.

Folliculitis Ulerythematosa Reticulata in Sisters. Presented by DR. FRANCIS E. SENEAR.

G. W., a woman aged 35, had acne of moderate degree during adolescence. For many years she has had a fine reticular scarring of the flush areas of the cheeks. She is not certain whether this antedates or follows the onset of acne. In the sternal region the patient presents a number of pigmented moles, these being for the most part of follicular location and varying in size from that of a pinpoint to that of a pinhead.

I. W., aged 27, is a sister of G. W. She likewise has a reticular scarring of the face and in addition has a large number of tiny papillomatous nevi scattered over the face, back and extremities. These nevi have been present since birth.

DISCUSSION

DR. THEODORE CORNBLEET: What interests me is the presence of comedos in the form of nevi, together with other lesions which might be described as follicular keratoses. These follicular keratoses and grouped comedos occurring in the same person lend support to the hypothesis that one of the early changes in comedo formation is a keratotic change high in the follicle.

DR. J. E. GINSBERG: I believe the lesion on the arm of the stouter sister (I. W.) is a naevus comedonicus unilateralis.

DR. S. ROTHMAN (by invitation): This condition has been described by Darier under the name atrophoderma vermiculatum and has been regarded as a nevus. Its familial occurrence has been described by W. Bruck. One finds comedos, dilatation of the pores and a peculiar atrophy causing a "worm-eaten" appearance of the cheeks. Ulerythema sycosiforme of Unna belongs to the group of chronic progressive follicular diseases with subsequent atrophy; this description does not apply to these conditions. Ulerythema ophryogenes, or keratosis pilaris rubra atrophicans, is a different condition.

DR. FRANCIS E. SENEAR: I showed these two patients together because it is generally accepted that this disease, to which many names have been given, is of nevoid character. It has no connection with ulerythema sycosiforme of Unna. It has been disputed whether the lesions are nevi or whether they are a peculiar scarring resulting from some type of folliculitis. As this condition occurred in sisters in this instance, a congenital possibility was considered. Each one of them has associated nevi. Some time ago one patient showed in the femoral region a number of papillomatous nevi which on clinical appearance resembled the dry lesions of the type seen on the sides of the neck. Those seem to have disappeared.

In answer to Dr. Rothman, the older woman shows no evidence of primary follicular or acneform lesions. Her sister did have some acne, but she is not certain whether this preceded or followed the development of the reticulate scarring. The presence of large numbers of comedos on the trunk and extremities is noteworthy. It has been pointed out that in a number of cases of this type there are no comedos but pseudocomedos. These are difficult to detach from the follicle. One cannot express them with the ease with which one can express an ordinary comedo. When I tried to express some on the arm, I could eventually squeeze them out, but they remained firmly attached to the follicle.

Naevus Anaemicus of Linear Configuration. Presented by DR. EARLE R. PACE.

M. S., a white woman aged 41, presents a banded zone of white macules extending from the base of the neck (right side) to the wrist. She states that it has been noted since childhood. The zone consists of pea-sized to dime-sized macules, closely set, forming a tapering reticulated band. It is widest at the root of the neck and courses laterally over the supraclavicular and deltoid areas and the lateral surface of the upper part of the arm, crossing the cubital fossa near the medial prominence, and distally on the forearm to the radial side of the wrist. The zone is about 10 cm. wide at the neck and tapers to 2 or 3 cm. on the forearm.

Rubbing with ice, application of heat, friction, trauma, sunlight or blushing does not change the color of the macules. Any of these stimulations readily produces hyperemia of the adjacent skin. There is no hyperpigmentation of the borders. There are no symptoms except a morbid fear of leprosy due to the careless remark of an acquaintance.

The Kahn reaction was negative on three occasions. The results of other laboratory tests were not pertinent. Histologic examination showed no apparent abnormalities of the blood vessels.

DISCUSSION

DR. M. R. CARO: I think that the diagnosis in this case must be made on clinical grounds, for a histologic diagnosis is difficult to establish. Some blood vessels were present in the tissue examined, and they seemed to be neither more nor less numerous than normal. The question always arises whether naevus anemicus is due to a paucity of blood vessels or to a vasoconstriction in the area. In this case the application of heat locally was not followed by a reddening of the skin, which shows that there probably were no constricted blood vessels in the affected area. The distribution of the nevus in this case is similar to that of

lesions in the cases of lichen striatus reported recently (Senear, F. E., and Caro, M. R.: Lichen Striatus, ARCH. DERMAT. & SYPH. **43**:116 [Jan.] 1941). There are many explanations for the distribution of lesions in linear streaks, but no one theory suffices to explain the localization in all cases. In the present case the distribution seems to fit in with a zosteriform pattern.

DR. EARLE R. PACE: I presented the case largely to record the results of biopsy. There seemed to be very few reported. The point Dr. Caro covered as to the scarcity of blood vessels or absence of dilators seems true because hyperemia cannot be produced by any method.

Dermatofibrosarcoma. Presented by DR. DAVID V. OMENS.

J. McT., an American laborer aged 46, presents on the left arm a patch the size of a half-dollar composed of variably sized nodules extending deeply, with the same characteristic nodular infiltration extending beyond the periphery. The lesion is firm to touch and insensitive. It has been present for fifteen years.

The histologic picture was compatible with the clinical diagnosis.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: In the few cases of dermatofibrosarcoma protuberans of Darier that have been observed at the clinic, the histologic picture has been essentially that of a simple dermatofibroma lenticulare with occasional mitotic figures. Histologically the sarcoma has been of a low grade, 1, on the basis of 4. As Dr. Senear pointed out, when one palpates the lesion, it extends much farther than its appearance would suggest. If these lesions are not excised widely, they keep recurring. I have encountered no case in which metastasis has occurred, although such cases have been reported in the literature.

DR. FRANCIS E. SENEAR: About the time Dr. Andrews, Dr. Willis and I reported a case of this disease (ARCH. DERMAT. & SYPH. **17**:821 [June] 1928), the original diagnosis having been made by Dr. Harold Cole at one of the annual meetings of this society, there was no report in the literature of definite metastases occurring with this disease, though there was 1 case in which there was a probable metastasis to the jugular region. In an article recently published from Dr. Cole's clinic the author (Binkley, G. W.: ARCH. DERMAT. & SYPH. **40**:578 [Oct.] 1939) referred to a number of cases found in the literature since that time in which metastases occurred. I am in accord with Dr. Montgomery when he says that in some of these cases the sarcomatous element is so slight that it is possible that it might be absent.

Histologically, the condition in this case is a true example of dermatofibrosarcoma protuberans.

Blastomycosis. Presented by DR. DAVID V. OMENS and DR. HAROLD D. OMENS (by invitation).

M. B., an American factory worker aged 41, presents an elongated infiltrated patch on the right side of the scrotum, the surface of which is composed of vegetations and scarring, with some pustulation occurring in the form of microabscesses. It has been present since August 1940. Microscopic examination of the pus revealed the budding organism.

In 1939 the patient was treated for the same condition. There were lesions on the upper lip, on the left elbow and on the left knee. They responded to local applications of copper sulfide, intravenous administration of iodides, oral administration of iodides in massive doses and roentgen therapy.

DISCUSSION

DR. HARRY R. FOERSTER, Milwaukee: Autoinoculation with the fingers from a preexisting lesion on the elbow probably accounts for the unusual location of

the blastomycotic lesion in this case. Because of the inguinocrural localization, it is important to recognize the clinical characteristics of blastomycosis as a means of differentiating this condition from granuloma inguinale, to which it bears superficial resemblance. The multiple lesions in this instance confirm the diagnosis.

DR. JAMES H. MITCHELL: The location of the lesion reminds me of a case described by Dr. Ormsby (Diseases of the Skin, ed. 5, Philadelphia, Lea & Febiger, 1937, p. 1070) in which a perfect Y was formed by the two inguinal folds, with the staff of the Y down the raphe. As I recall, the external genitalia were destroyed eventually.

DR. OLIVER S. ORMSBY: I think that the papillomatous elongated lesion is typical of this disease. I have had several patients with similar lesions in that region.

DR. EDWARD A. OLIVER: I have treated several patients with this condition at the Veterans Administration facility, Hines, Ill., by means of iontophoresis with copper sulfate. In stubborn cases the end results have been excellent. In 1 case an especially recalcitrant condition was treated by Dr. E. M. Smith Jr. at St. Luke's Hospital with the cutting current with a good result.

DR. E. M. SMITH JR. (by invitation): Since the pathologic changes of this condition are superficial, mostly in the epidermis, the use of the electric cutting current will remove the lesions. The wire loop can be used to curet away the granulomatous material, leaving firm healthy tissue. The use of a coagulating current (as in the case of a destructive antiseptic) produces too much damage to the healthy structures and thus defeats its purpose. Large doses of potassium iodide inhibit the growth of the invading organism.

DR. THEODORE CORNBLEET: Clinically the condition looks like a localized infection of the skin, but there is something in the history that may be suggestive of a systemic infection. The patient says that the lesion on the knee began with a boil or abscess, and on top of that he noticed that vegetations occurred. Then the lesions on the elbows occurred shortly after he had some teeth extracted.

DR. ERWIN P. ZEISLER: It occurred to me that sulfanilamide, which has been effective in deep-seated lesions of the fingers, such as actinomycosis, might be worth trying.

DR. DAVID V. OMENS: Primarily I showed this patient because one with blastomycosis had not been shown before the society in two or three years. I have seen this man since 1939, at which time he had a blastomycotic lesion on the upper lip and one on the left elbow and knee. They responded to iodides administered internally and to roentgen rays and copper sulfate applied locally. Six or eight months later he consulted me for treatment of the lesion on the scrotum.

I am grateful to Dr. Zeisler for the suggestion of using sulfanilamide. I have used various applications without any results. I last used local applications of a solution of formaldehyde, which seemed to have good effects. I stopped using it so as to show the patient at this meeting. I believe solution of formaldehyde applied locally and sulfanilamide given internally might bring about a good result.

Sickle Cell Anemia Associated with Chronic Ulcers of the Leg and Hyperkeratotic Plaques. Presented by DR. E. M. SMITH JR. (by invitation) and DR. I. A. LEWE (by invitation).

R. D., a Negro aged 39, from the service of Dr. Edward A. Oliver, Northwestern University Medical School, was first seen in the dispensary of St. Luke's Hospital on Nov. 2, 1937, with an ulcer on the anterior surface of the left leg which had followed an injury from falling on a stone step two weeks before. Kahn and Wassermann reactions were reported negative. Treatment

consisted of topical applications of ammoniated mercury ointment, oral administration of potassium iodide and nine intramuscular injections of bismuth subsalicylate; there was partial healing while under observation, but the lesion broke down again. This time applications of paste of zinc oxide (Unna's boot) resulted in almost complete healing after several months.

The patient was seen again on July 1, 1938. The ulcer was closed over, and again the serologic reactions were negative.

The ulcer broke down a second time in July 1938 and finally healed after several months of therapy, which included Unna's paste boots and a period of hospitalization.

In December 1940 a number of new ulcers appeared on the left leg, most of which are closed at present.

Examination reveals a superficial, somewhat punched-out ulcer, 1 cm. in diameter, on the posterior aspect of the left leg. The base is reddish and covered with a seropurulent exudate. On the lateral and posterior surfaces of the leg above the ankle are multiple healed ulcers. On the anterior surface, marking the site of the original ulcer, is a brownish hyperkeratotic plaque with a surrounding area of mottled depigmentation.

In addition, the patient presents numerous dark brownish hyperkeratotic lichenified plaques on the posterior surfaces of both thighs and on the medial aspect of the left leg and ankle. The latter condition is pruritic and is of only several months' duration. There are many smooth atrophic pigmented scars on the calf of the right leg and a few on the left leg resulting from an old burn. On the trunk, thighs and arms are many pigmented macules which the patient states are the residua of an acute eruption in 1937. The balance of the physical examination reveals icterus of the scleras, shotty lymphadenopathy of the axillas and groins and a systolic cardiac murmur.

The family history is not significant.

Wassermann and Kahn reactions were negative on three occasions, the last time on Feb. 28, 1941. The urine was normal on three occasions. Examination of the blood on Feb. 3, 1938 gave the following results: hemoglobin, 21 Sahli units, 4.5 Gm. per hundred cubic centimeters (26 per cent); red blood cells, 1,570,000, and white blood cells 9,600, with a differential distribution of polymorphonuclear neutrophils 69 per cent, with 2 per cent immature, lymphocytes 24 per cent, monocytes 2 per cent, eosinophils 2 per cent, basophils 1 per cent. The red blood cells were pale, and there were slight polychromatophilia, a few microcytes, several macrocytes, an occasional poikilocyte and 12 megaloblasts per hundred white cells counted. The volume index was 1.14. On July 8, 1938 another examination of the blood revealed several sickle cells, and on March 2, 1941 sickle cells comprised 15 to 20 per cent of the red blood cells.

On Feb. 3, 1939 chemical examination of the blood showed total nonprotein nitrogen 35.3 mg. per hundred cubic centimeters, icterus index 5 units and the result of a van den Bergh indirect test slightly positive. On March 10, 1941 the icterus index was 100 units.

Roentgenograms on March 17, 1941 showed a slight degree of osteoporosis of the skull and long bones. A roentgenogram of the chest showed an enlarged heart and evidence of an old pleurisy infection in the base of the right lung.

Histologic examination on March 10, 1941 of a specimen taken from one of the plaques showed an irregular acanthosis of the epidermis with moderate hyperkeratosis. The blood vessels of the upper corium were dilated, and there was a scanty perivascular infiltration of lymphocytes and fibroblasts. A specimen from the edge of an active ulcer showed an acanthotic edematous epidermis with prolonged irregular rete pegs. The ulcer was superficial, and the underlying corium was filled with a rather dense infiltrate of polymorphonuclear leukocytes, small lymphocytes, epithelioid cells and a moderate number of plasma cells. The blood vessels were increased in number and dilated and showed swelling of the endothelium.

Sickle Cell Anemia with Ulcer of the Left Ankle. Presented by DR. MICHAEL H. EBERT.

J. R., a Negress aged 32, states that she had always been well until seven years ago, when there developed acute polyarthritis of the metacarpophalangeal joints of the right hand, the left knee and the ankle, with a temperature of 106 F. She also had jaundice with yellow scleras and finger nails, followed by the formation of an ulcer over the left tibia, which persisted for about six months. A year later she had an attack of nausea and persistent vomiting with intense jaundice. She was confined to bed for one month, at which time the diagnosis of sickle cell anemia was made. During the past six years she has had numerous attacks of jaundice with absence of clay-colored stools or highly pigmented urine. In September 1940 the skin on the left leg in the area of the old scar broke open spontaneously after swelling of the ankle but preceded by several days with yellowish scleras, dyspnea on exertion and fatigue. The patient does not know of any member of her family with the same or a similar condition.

On examination the patient is well developed and nourished with no discomforts. There is a noticeable bilateral exophthalmos with only a suggestion of yellowness of the scleras. There is a deformity in abduction of the proximal phalanx of the right first metacarpophalangeal joint, with a grating sensation on motion. Grossly the left knee is larger than the right one with limited flexion and crepitus on motion. On the medial surface of the left ankle is a palm-sized scaly dry area with a pinkish atrophic scar in the center surrounded by a wide zone of hyperpigmentation. At the distal portion of this area is a quarter-dollar-sized lesion covered with a dried crust which when removed leaves a sloping ulcer. A similar but more superficial-looking crusted ulcer is present over the left lateral malleolus. The spleen and liver are not palpable.

Laboratory examinations made during the first week of March 1941 gave the following results: The urine was essentially normal. The icteric index was 34. Examination of the blood showed hemoglobin, 45 per cent; red blood cells, 2,500,000; white blood cells, 13,750; normal platelets; a differential distribution of polymorphonuclear leukocytes 76 per cent, eosinophils 2 per cent, basophils 2 per cent, lymphocytes 17 per cent and monocytes 3 per cent; anisocytosis, 2 plus; poikilocytosis, 3 plus. A sickle cell preparation showed 50 per cent sickling in twenty-four hours. The fragility test showed partial hemolysis at 0.36 per cent and complete hemolysis at 0.26 per cent. The Kahn reaction was negative. Chemical examination of the blood showed nonprotein nitrogen 26 mg. per hundred cubic centimeters and creatine 1.3 mg. A roentgenogram of the chest showed enlargement of the cardiac shadow both to the left and to the right and also a suggestion of a slight amount of infiltration in the lateral portion of the first anterior interspace on the right side.

Treatment to date has consisted of rest in bed, administration of ferrous sulfate orally and blood transfusions.

DISCUSSION OF CASES OF SICKLE CELL ANEMIA WITH ULCERS OF THE LEG

DR. J. E. GINSBERG: I saw the microscopic slides of Dr. Smith's patient. The histologic picture of the superficial ulcer is simply nonspecific and that for the area of hyperkeratosis is not particularly characteristic of any disease.

DR. MAURICE OPPENHEIM (by invitation): I know little about sickle cell anemia. It does not occur in Austria or Germany; there is no Negro population.

DR. EDWARD A. OLIVER: My attention was called to this type of anemia several years ago. A Negress in the outpatient clinic at St. Luke's Hospital had an ulcer of the leg that resisted all treatment. It was finally decided that it was possible that she had sickle cell anemia, and examination of smears of her blood showed that was the case. Even then there was difficulty in healing the ulcer, as

patients with this condition do not respond to treatment readily. This was brought out in an excellent paper read before the American Dermatological Association last year (Cummer, C. L., and LaRocco, C. G.: Ulcers of the Legs in Sickle Cell Anemia, ARCH. DERMAT. & SYPH. **42**:1015 [Dec.] 1940). This type of anemia is almost exclusively seen in Negroes. I am glad that these patients were shown, because now the members present will be more alert to recognize the condition.

DR. ERWIN P. ZEISLER: It seems to me that 1 patient had an eruption that looked much like prurigo nodularis. There were pruritic lesions on the extremities and arms.

DR. MICHAEL H. EBERT: It is interesting to note that sickle cell anemia was first described in Chicago as a clinical entity by Dr. James B. Herrick. I consulted the excellent article by Cummer and LaRocco before presenting this case and found it full of valuable information. My patient, in addition to the ulcer on the leg, presented several of the other conditions that these authors described. They pointed out that a relatively high percentage, approximately 8 per cent, of Negroes have sicklemia; this means there is a sickling of the red blood cells on staining. However, in only a small percentage of these persons does true sickle cell anemia develop with the crisis characteristic of this condition. This patient presents the peculiar greenish discoloration of the scleras that Cummer and LaRocco described, as well as arthritic manifestations in several of the joints. She has a definite enlargement of the heart with symptoms of heart disease. The question might well be asked as to whether there is any evidence that ulcers of the leg have anything to do with sickle cell anemia. It is well known that Negroes are particularly liable to ulcers of the leg on a syphilitic basis, so the mere association of an ulcer with sickle cell anemia does not mean that the anemia is the cause. However, Cummer and LaRocco made a study of the literature and showed that in other types of anemia, like pernicious anemia and chlorosis, the percentage of ulcers was nothing like that found in sickle cell anemia.

Pityriasis Lichenoides Chronica. Presented by DR. MAURICE OPPENHEIM (by invitation) and DR. D. COHEN.

A. R., a white man aged 23, presents a pruritic eruption which began two years ago. The areas affected include the extensor surfaces of the extremities, more than the flexor surfaces, and the trunk. The face, scalp and palms are not involved. The lesions consist of macules and papules varying in size from that of a pinpoint to that of a dime. Some are light brown and others brown-red. The surfaces are branlike with desquamation. There is no tendency to confluence. There is no involvement of the lymphatic glands or of the mucous membranes.

Von Pirquet and Mantoux tests gave negative results. Histologic examination revealed no enlargement of the epidermis; in several places there was decided parakeratosis. There was no stratum granulosum, acanthosis, spongiosis or reticular degeneration. The border between the epidermis and the cutis was not sharp. There was round cell infiltration and partial homogenization of the subepithelial border.

DISCUSSION

DR. OTTO H. FOERSTER, Milwaukee: The patient presented an unusual clinical picture that requires and merits more careful consideration than I could give it. However, if this condition is an example of pityriasis lichenoides chronica, it is not the classic form with which I have become familiar. According to the appearance in this case, the condition might perhaps be better designated by the term psoriasiform and lichenoid exanthem, as used by Jadassohn, than by the term given by Juliusberg to this disease. I noticed complete absence of leukoderma of the neck, which is present in a considerable percentage of cases of

true pityriasis lichenoides chronica. Also, I did not observe the characteristic type of scale which covers the small papules like a lid. The absence of both of these features might be used as differential diagnostic points.

DR. JAMES H. MITCHELL: I should like to ask Dr. Oppenheim about the itching. The patient described to me intense itching which kept him awake at night, which I believe is unusual in pityriasis lichenoides chronica.

DR. MICHAEL H. EBERT: Since some of the obscure unusual keratotic diseases like pityriasis rubra pilaris and Darier's disease seem to be affected by large doses of vitamin A, I suggest that such therapy might be tried in this case.

DR. MAURICE OPPENHEIM (by invitation): We presented this case largely for purposes of differential diagnosis. The histologic picture led to the diagnosis of pityriasis lichenoides, which belongs in the group of parapsoriasis. It is interesting to note that in a case in which there is an exactly similar clinical aspect the histologic examination shows so little that is characteristic. The observations are only parakeratosis, edema of the papillae and round cell infiltration.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I was glad to have Dr. Oppenheim mention the difficulties in diagnosis. Histologically differences in types of parapsoriasis are not as sharp or clearcut as the textbooks would lead one to believe.

Lupus Erythematosus Disseminatus. Presented by DR. DAVID V. OMENS.

D. M., a white woman aged 19, states that three months ago she noticed a reddened area on the bridge of the nose. The lesion did not heal; so one month later she consulted a physician, who administered ultraviolet therapy biweekly for three weeks. The lesion began to spread rapidly over the cheeks and around the eyelids and became painful. She consulted a second physician, who gave her pills and a salve. No result having been obtained with this treatment, she came to the hospital.

She had a splenectomy at the age of 14 because of persistent nosebleeds. There is no previous history of cutaneous trouble or of tuberculosis in the patient or in her family.

Examination shows a diffuse erythema on the nose, cheeks and eyelids, with similar smaller areas on the sides of the chin. The hard palate shows an erythematous and grayish white patch, the size of a quarter, in the midline, with a smaller area on the right buccal mucosa. Over the right lower rectus muscle is an infiltrated palm-sized area with similar pinhead-sized lesions on the finger tips.

Wassermann and Kahn reactions were negative. The urine, a blood count and a roentgenogram of the chest were normal.

DISCUSSION

DR. S. ROTHMAN (by invitation): The eruption seems to belong to the chronic discoid form with acute exacerbation.

DR. EDWARD A. OLIVER: I prefer to label this condition acute disseminated lupus erythematosus. While this girl may not be seriously ill today, I predict that it will be only a short time until she is.

DR. MICHAEL H. EBERT: I hardly believe that this condition is a simple disseminated discoid type of lupus erythematosus. The characteristic changes of disseminated lupus erythematosus are present at the base of the nail. She had a macular edema in the palms and a few other places. I think the condition is a subacute disseminated lupus erthematosus. It may have originated as the discoid type, but something happened and it has become disseminated.

DR. FRANCIS E. SENEAR: I think the condition is a classic example of a type that is becoming disseminated and may be spoken of as subacute because

there is no leukopenia, the patient is not ill and there is no albuminuria, which is commonly found in the acute type. I think it is important to look on this as a disseminated type. The patient may die as a result of the disease sooner or later, and one would feel much more comfortable if one had looked on it as a serious disseminated type of lupus erythematosus rather than the discoid type that was disseminating.

DR. DAVID V. OMENS: I do not believe the condition is an acute disseminated lupus erythematosus. For one thing, the patient is in good condition. She is not as sick as one would expect in acute lupus erythematosus. When I first saw her last week her skin was much worse than it is today.

NOTE.—The patient died about two weeks later.

Neural Leprosy with Tuberculoid Lesions. Presented by DR. STEPHEN ROTHMAN (by invitation) and DR. MAXIMILIAN E. OBERMAYER.

J. J., a Chinese man aged 31, was first seen seven months ago with the complaint of loss of the terminal phalanges of three fingers of the right hand.

Neural leprosy with tuberculoid lesions.

He claimed that the process had started only a year previously. He stated that a generalized eruption which was also present was of only one week's duration. The patient emigrated to the United States from China twelve years ago and, except for a short period spent in Detroit, has lived in Chicago ever since.

Examination showed that the terminal phalanges of the ring, index and middle fingers of the right hand were absent. The skin of the fingers was erythematous, and erosions and ulcerations were present. The ear lobes were slightly enlarged.

A generalized papulosquamous eruption was present on the trunk and the extremities. The copper brownish lesions varied in size and shape, were distinctly elevated and formed bizarre patterns. The involved areas and the dorsum of the right hand were hypesthetic.

A smear of material from a nodule on the ear lobe showed lepra bacilli. Acid-fast stain of the biopsy specimen from the ear lobe also showed these organisms.

Histologic examination of one of the cutaneous lesions showed a granuloma which consisted mainly of epithelioid and a few lepra cells.

The urine was normal. A blood count was normal, and Kolmer and Kahn reactions of the blood serum were negative.

The patient has received thirty weekly injections of ethyl chaulmoograte, 3 cc. intramuscularly, with gradual involution of the lesions.

DISCUSSION

DR. A. W. STILLIANS: There was a case many years ago at the Cook County Hospital in which there was loss of the fingers of both hands but no other lesions. This case is the second I have observed in Chicago.

DR. OTTO H. FOERSTER, Milwaukee: Of special interest are the striated or bandlike atrophic lesions on the arms which represent a form of atrophy in leprosy that was, I believe, first described by Dr. Oppenheim many years ago.

DR. MAURICE OPPENHEIM (by invitation): Conditions such as this one were described by me as dermatitis leprosa atrophicans (*Wien. klin. Wchnschr.* **16:** 615, 1903; *Arch. f. Dermat. u. Syph.* **68:**81, 1904) after my return from the Indian Leper Asylum Matunga near Bombay, India. I found there among 375 patients with various types of leprosy almost 20 who showed the typical changes seen in dermatitis atrophicans chronic progressiva (atrophia idiopathica cutis). The skin folded and wrinkled like cigaret paper; the veins were translucent; the raised folds remained a long time before flattening, and there was a fine desquamation. This condition of the skin was present over almost the whole body. The histologic picture was the same as in dermatitis atrophicans diffusa progressiva; lepra bacilli and lepra cells could be found in the infiltration.

Zosteriform Lichen Planus. Presented by DR. HERBERT RATTNER and DR. MAURICE DORNE.

F. W., a white woman aged 44, when first seen on March 6, 1941 presented an eruption of five weeks' duration. It consisted of confluent, flat-topped, violaceous, angular, shiny papules. The lesions were grouped in a bandlike arrangement in three areas: the left forearm and arm, the left side of the abdomen and the left thigh. Each band followed the transverse lines of the skin. When she was seen one week later the eruption had undergone so much involution as to suggest a diagnosis of lichen striatus, but the histologic picture is that of lichen planus.

DISCUSSION

DR. FRANCIS E. SENEAR: I feel that the condition is certainly a linear lichen planus. As the history pointed out, much of the eruption has disappeared, and there might be some confusion with lichen striatus, but the lesions that are still active in a quarter-dollar-sized patch on the outer aspect of the thigh are still infiltrated, far beyond what one might see in lichen striatus.

DR. THEODORE CORNBLEET: Zosteriform eruptions may be seen in leukemic states. It may be worth while to examine this patient's blood.

DR. MAURICE DORNE: When I first saw this patient the possibility of lichen striatus presented itself because of the unilateral and linear distribution of the

eruption, but this was suggested even more after a week of using soothing local applications, when there was decided involution. However, the histologic section by that time gave a picture of lichen planus.

Lichen Urticatus. Prurigo? Presented by DR. FRANCIS E. SENEAR.

H. L., a Negro boy aged 3 years, has had an eruption on the forehead and on the extensor surfaces of the arms and legs for the past six months. The lesions begin as "tiny bumps" which itch intensely and which after scratching gradually increase in size.

The patient's mother, now 28 years old, had a similar condition which began when she was about 3 years of age. She was seen in September 1928, at which time she complained of "bumps" on the legs which had been present to greater or lesser extent for the previous twelve years. The eruption was always worse in the summer, and the lesions were accompanied by intense itching. She stated that her lesions began as reddish papules and that after they had been scratched, they gradually grew larger to form nodules. Examination at that time showed on the legs, chiefly the anterior aspects, on the sides of the trunk and on the forearm a large number of excoriated papular lesions, some of which were so large and so elevated as to be nodular. The surfaces of some of these lesions were smooth, while others presented scales or scaly crusts. The mother was seen on this one occasion only, and when she returned with her child a few days ago, she stated that her eruption had persisted until she was 23 years of age, when it had disappeared spontaneously.

DISCUSSION

DR. MAURICE OPPENHEIM (by invitation): I think Dr. Senear is right, that this case is one of prurigo mitis. Some of the nodules show secondary infection. The location on the extensor surfaces of the extremities is the same and the clinical aspect of the nodules is identical with those of prurigo.

DR. M. E. OBERMAYER: I cannot agree with the diagnosis of prurigo. The initial lesion of prurigo is a small papule which at first can be felt by palpation rather than seen. Once fully developed it is destroyed by scratching, because the patient finds that destruction is the only means of relieving his intolerable pruritus. Therefore, only rarely can intact lesions be observed. The skin of this patient has shown no evidence of scratch marks. I questioned the mother specifically as to the duration of the individual papules and was told that the same lesions had been present for weeks if not months. I cannot agree either with the diagnosis of lichen urticatus. The persistence of the individual lesions alone rules out that diagnosis. Besides, the papules did not exhibit the clinical features of lichen urticatus. Some of them, especially on the hands, were rather flat topped and shiny. If the histologic picture—I had no opportunity to study the slide—is at all compatible with lichen planus, I suggest an atypical form of this disease for the diagnosis.

DR. OLIVER S. ORMSBY: The similarity between lichen urticatus and prurigo in its early stages is often striking. A period of observation will distinguish between the two. Colcott Fox considered lichen urticatus the classic urticaria of childhood. In order to settle the question of identity of the two diseases, he kept a number of patients with lichen urticatus under observation over a period of ten years, and in none of them did prurigo develop. The urticarial wheal of lichen urticatus is usually present only at night, while during the day an inflammatory crusted papule remains. In its early stages prurigo is also accompanied by some urticarial lesions. In time in cases of this kind the characteristic papules develop, and they are accompanied by thickening of the skin, pigmentation and adenopathy.

DR. EDWARD A. OLIVER: In differentiating the condition in this case from prurigo, it might be interesting to try the treatment suggested by Hallan. He has pointed out that a patient with lichen urticatus invariably recovers without treatment if he sleeps in the hospital, even if his food is brought from home or if he spends the day at home. If, however, he sleeps at home, even if he spends the day in the hospital, there is a relapse. Hallan considers lichen urticatus to be a manifestation of allergy to some substance encountered when the child sleeps at home. It would be interesting to have this boy sleep in a hospital bed for a few nights. A diagnosis might be arrived at in this way.

DR. FRANCIS E. SENEAR: I am glad to find that there are others who have had experience with prurigo mitis who are not in agreement as to the diagnosis in cases of this type. Because of the limited experience with prurigo in this country, it has been found that when a case is presented with this diagnosis, the diagnosis has been disputed by physicians who have seen many examples of this condition in Continental clinics. I saw this patient in the office and asked Dr. Oliver to see him. We both thought of lichen planus and prurigo as possibilities. I think it is worth commenting that the mother had the same eruption from her third to twenty-third year. I saw her in 1927. At that time she had indurated lesions, such as the boy presents, but they were so large and so hyperkeratotic that they could be almost spoken of as lesions of prurigo nodularis. The mother stated definitely that her eruption was worse, more extensive and more pruritic, during the summer. That would fit in with my conception of lichen urticatus.

DR. MICHAEL H. EBERT: The mother said she had another child that was confined to the hospital with eczema. While the condition was said to be a classic eczema, she stated that it looks much like this patient's condition.

DR. FRANCIS E. SENEAR: I did not see the other child. I asked her if she had other children with a similar eruption and was told that she did not. Two of the discussers asked about the histologic report. There were no slides presented.

Verrucae Following Exposure to Sunlight. Presented by DR. FRANCIS E. SENEAR.

M. L., a woman aged 39, spent the month of August 1940 in the hospital after an automobile accident. During this time she had been instructed to sit in the sun parlor of the hospital as much of the time as possible, and for ten days she spent a great deal of time exposed to the sun's rays. Just before she left the hospital she noticed that brownish spots were developing on the chest. These have gradually increased in number. About five months ago similar lesions appeared on the forehead, and about three months ago a number of lesions also appeared on the extensor surfaces of the arms.

The lesions on the chest are confined to the V area and appear as flat-topped, sharply circumscribed, pinhead-sized to split pea–sized macules or papules. Some of these are of normal skin color; some have horny verrucous surfaces, and others, which are brown, resemble somewhat verrucous nevi.

DISCUSSION

DR. OTTO H. FOERSTER, Milwaukee: The clinical picture is rather confusing, with an intermingling of typical lesions of plane verrucae and a number of flat scaling lesions that I consider to be keratoses following actinic exposure.

DR. CLARK W. FINNERUD: I thought, because of the verrucous character of some of the lesions and the fibromatous character of others, that the condition could probably be classed as epidermodysplasia verruciformis. I do not know what relation the actinic rays would have to it.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I agree with Dr. Finnerud that this condition could be epidermodysplasia verruciformis of Lewandowsky and Lutz. It is most unusual for verrucae to develop in areas limited essentially to those exposed to sunlight.

DR. MORRIS WAISMAN (by invitation): This case could be one of epidermodysplasia verruciformis, and it is not remarkable for the disease to appear at this patient's age. Moreover, although the disease is often generalized, a restricted distribution of lesions is also a feature in other cases cited in the literature. The flat-topped verrucous papules may appear only on the extremities or even on a single extremity. The relation to physical trauma, such as exposure to sunlight, has been described in some instances. The diagnosis is established microscopically by the characteristic vacuolation in the epidermis and the broadening of the stratum granulosum.

One condition important to distinguish from epidermodysplasia verruciformis, both clinically and histologically, is verruca plana juvenilis, and observers such as Hoffmann, Gans, and Kogoj have expressed the opinion that they are one and the same disease. On the strength of material studied so far, Dr. Montgomery and I believe that histologically, at any rate, verruca plana and epidermodysplasia present almost, if not quite, identical pictures. It is tempting to believe, however, that because of their different behavior clinically (persistence of lesions, rebelliousness to treatment, occasional supervention of epitheliomas and failure of inoculation experiments in epidermodysplasia verruciformis) they may represent separate entities.

In this particular case I feel that the lesions are probably those of seborrheic, or senile, verrucae. I was wondering, however, if another diagnostic possibility may not be one of the forms of cutaneous papillomatosis described by Gougerot and Carteaud (*Arch. f. Dermat. u. Syph.* **165**:232-267, 1932).

Precocious Syphilis. Presented by DR. S. WILLIAM BECKER and DR. M. E. OBERMAYER.

F. T., an American man aged 25, was first seen six weeks ago. He stated that he contracted syphilis eleven months ago while serving with the United States Navy. He claims that in spite of the usual prophylactic measures an ulcerative lesion which was indurated developed on his penis followed by swelling of the regional lymph nodes. Dark field examinations performed by the ship's surgeon showed no spirochetes until the ninth trial. In spite of treatment with mapharsen and a bismuth compound, which was begun early, a generalized impetiginous syphilid appeared one month later. The lesions continued to appear, and after two more months additional lesions developed on the legs, which were nodulo-ulcerative. The reaction to serologic tests of the blood remained negative until a month after the appearance of the generalized syphilid, when it became and has remained strongly positive. Cutaneous syphilids continued to appear in spite of treatment in a hospital, where neoarsphenamine was administered after three courses of mapharsen and a bismuth compound had proved ineffective.

Examination discloses an impetiginous syphilid of the scalp, face, trunk and genitalia. Atrophic scars, serpiginous in outline and surrounded by hyperpigmentation, were present on the buttocks and legs. Nontender enlarged lymph nodes are present in the neck, in the axillas and in the inguinal region.

The spinal fluid was normal.

DISCUSSION

DR. DAVID LIEBERTHAL: I encountered cases similar to this when soldiers returned from the Philippine Islands after the Spanish-American war who had contracted the disease from natives there as this patient has. About a year ago I was in consultation with a colleague about a patient who had been infected about eighteen months before and had been receiving courses of injections of

mapharsen and a bismuth preparation. His symptoms subsided; the Wassermann reaction of the blood became negative, and he was permitted to marry. A few weeks thereafter a copious papulopustular eruption developed and the Wassermann reaction was positive. In spite of repetition of mapharsen and bismuth therapy no change in his condition took place. I saw him then, agreed with the diagnosis and advised a change of treatment to mercury and potassium iodide, which changed the picture completely within several weeks. According to his physician's report, the patient continues to be in good condition. Considering the treatment which I employed in the cases of many years ago and in this later one, I suggest that Drs. Becker and Obermayer try the mixed treatment with mercury and potassium iodide in their case.

DR. OLIVER S. ORMSBY: Occasionally a patient presents a combination of late and early syphilis. Dr. Mitchell photographed such a patient for my collection. This condition is classed as the corymbose syphiloderm and is often a relapsing one. It is usually composed of a large papule surrounded by a group of small papules. It may be that in this case the treatment partially cleared the condition and the patient now presents a mixed type of both early and late syphilids.

DR. MICHAEL H. EBERT: I should like to ask the presenter if old arsphenamine was used in this case.

DR. M. E. OBERMAYER: Dr. Becker and I thought this condition a good example of precocious syphilis. The old problem now arises whether to ascribe the abnormal course of the disease to a particular strain of spirochetes or to an unfavorable reaction to an ordinary infection on the part of the person. I rather believe in the latter explanation, and though the patient does not by any means present the cachectic appearance ordinarily expected in persons who have precocious syphilis and otherwise seems to be in excellent health, he is addicted to chronic alcoholism, which may account for the precocious character of the disease.

Old arsphenamine has not been used yet. Since the patient had received three courses of mapharsen combined with a bismuth compound and one course of neoarsphenamine without result, it was thought best to hospitalize him and to attempt to alter his reactivity by means of nonsyphilitic therapy. He was given a full course of fever treatment in the form of administration of typhoid-paratyphoid vaccine combined with daily general ultraviolet irradiations in slowly increasing doses. During the first few weeks of this form of treatment lesions continued to develop, but recurrences ceased later. Last week antisyphilitic therapy with sobisminol mass was begun, and it seems that the patient is responding now to specific treatment, though it is too early to draw definite conclusions.

A Case for Diagnosis (Premature Synostosis or Periosteal Thickening as a Residue of Some Previous Periostitis Secondarily Involving the Skin?). Presented by DR. JAMES R. WEBSTER and DR. R. H. SCULL (by invitation).

V. C., a woman aged 28, states that at the age of 10 years she had a streak of white hair in the midline of the frontal area. This was later associated with a slightly elevated ridge. Often there were violent headaches and a crawling sensation. The ridge was cauterized. Later this ridge became a depression which progressed downward from the hair line, with hyperpigmentation, at the rate of about ½ inch (1.3 cm.) a year to its present location on the bridge of the nose. She also states that the width has increased since the process began.

Examination reveals a linear hyperpigmented depression in the midline of the forehead extending from the scalp to the bridge of the nose.

The results of laboratory tests, including Wassermann and Kahn tests, were negative except for the roentgenograms, which showed a thickening sometimes seen in premature synostosis or a periosteal thickening as a residue of a previous periostitis.

DISCUSSION

DR. OLIVER S. ORMSBY: The lesion here suggests the saber blade type of scleroderma. In this form of scleroderma the lesion may begin on the forehead and extend upward and downward or begin in the scalp and extend downward and also farther back, but it always extends one way or another. In most of the cases the lesion ends either in the brow or on the top of the nose between the brows in a sharp point. As it extends over the forehead and scalp the lesion becomes broader and may become 2 inches (5 cm.) or more broad at the crown. In the early stages it is indurated, and later it becomes soft. It is brown-yellow. After the lesion has undergone resolution and atrophy there remains a deep depression that involves not only the skin but the bone. In this case the lesion is not pointed and is of equal breadth throughout. There is no doubt that there is atrophy of the bone.

DR. JAMES R. WEBSTER: It is unfortunate that information is not available as to how this patient looked ten or fifteen years ago, because at present the condition is purely an atrophy. It is not my conception of the type of atrophy that is the end stage of scleroderma. Even if scleroderma had become burned out, so to speak, I think there would be more of a hidebound character than is shown by this lesion, which is definitely soft and not adherent to the underlying structures.

Linear Lichen Planus; Ichthyosis Hystrix; Linear Verrucae? Presented by DR. JAMES R. WEBSTER and DR. R. H. SCULL (by invitation).

P. H., a youth aged 17, states that four months ago a papule appeared on the upper third of the outer aspect of the right thigh. It grew larger and became crusted. This was followed by several similarly placed papules extending in more or less linear fashion down the thigh and leg. There was slight itching associated with the lesion.

Examination reveals several hypertrophic, warty lesions with some tendency to grouping, following a more or less linear arrangement and extending from the upper third of the lateral surface of the thigh down to and including the leg. The patient's father has the same type of eruption.

The Wassermann and Kahn reactions were negative.

Histologic examination of a specimen from the upper part of the thigh showed hyperkeratosis with some parakeratosis, hypertrophy of the stratum granulosum and acanthosis. The corium showed a subepithelial infiltrate in one area, not especially dense or well defined. There was a space formation between the infiltrate and the epithelium.

DISCUSSION

DR. FRANCIS E. SENEAR: I could not see anything in the clinical picture that suggested lichen planus. The microscopic section showed nothing to conform to such a diagnosis. The question always arises in cases of this type, if the condition has been present for only a few months, as to whether or not the lesion is a late-developing nevus. Such cases cause a great deal of clinical confusion. Many may recall the young girl shown at the meeting of the American Academy of Dermatology and Syphilology who had psoriasiform lesions extending down the forearm. When I first saw her she had huge, raised, white scales, grossly heaped, and without hearing the history I made a diagnosis of ichthyosis hystrix. Other members of the staff made a diagnosis of linear psoriasis. After hearing the history of recent development I still insisted that the condition was a linear nevus. The histologic picture was reported by Dr. Caro as typical of psoriasis. When this case was presented at the meeting of the Academy a few weeks later the diagnosis was given as linear psoriasis. I recall hearing a number of observers wondering on what findings the idea of linear psoriasis was based, since they all felt that the condition was a linear nevus. As linear nevi not infrequently develop some years after birth, I am inclined to look on the condition in the case just presented as a linear nevus.

DR. M. R. CARO: Histologically the absence of pathologic changes in the upper part of the corium eliminates linear lichen planus as a possibility. The histologic picture is consistent with the diagnosis of ichthyosis hystrix.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: The histopathologic picture is consistent with ichthyosis hystrix. In this condition there is increase in the granular layer, which is not the case in ordinary ichthyosis.

LEONARD F. WEBER, M.D., *President*

MICHAEL H. EBERT, M.D., *Secretary*

April 16, 1941

A Case for Diagnosis (Sclerodactylia?). Presented by DR. HARRY M. HEDGE.

Mrs. C. B., a white woman aged 52, a cashier, was well until ten weeks ago, when she noticed that her hands became numb and tingled for a few days and then became normal. She had been cleaning a hat and some clothing with a preparation called "Energy Napthene," of which a teaspoonful of the crystals was dissolved in a gallon (3.8 liters) of water. There was no irritation immediately following the use of this cleaner, but after a few days there was an interdigital desquamation resembling erosio interdigitalis blastomycetica. The fingers became stiff, and the patient was unable to pick up money to make change, being compelled to slide it out from the cage with her stiffened fingers. The tingling and numbness were followed by swelling, redness and some burning pains. She also had a condition simulating arthritis of the fingers, of the elbow and shoulder joints and of the knees, for which she used various local preparations.

The onset of the menopause was nine years ago. She has gained some weight in the last year. During the last two years she has had two attacks of pyuria and hematuria, which lasted only a few days. The teeth have all been extracted. The thyroid is fairly easily palpated. There are slight external hemorrhoids. Both hands are puffy and shiny with some limitation of motion in the fingers.

Urinalysis showed a faint reaction for albumin and 1 to 3 pus cells to the microscopic field. A blood count showed 4,750,000 red blood cells and 5,700 white blood cells; there was 16.5 Gm. of hemoglobin per hundred cubic centimeters of blood. The basal metablic rate was + 6 per cent. The sedimentation rate was 10 mm. per hour. Roentgenograms of the hands and chest were normal.

DISCUSSION

DR. S. W. BECKER: I believe that the patient has a type of scleroderma characterized by fibrosis of the deeper tissues around the joints rather than of the superficial tissues. The skin of the palms seems to be thin rather than thickened. Has a neurologic examination been made to determine whether there is any other cause for her apparent paresthesias?

DR. LOUIS A. BRUNSTING, Rochester, Minn.: Because of the paresthesias I recommend a neurologic examination to consider the question of peripheral neuritis, related possibly to intoxication by lead or arsenic. In this case there seems to be a lack of acroasphyxia, which usually precedes the development of acrosclerosis or sclerodactylia. It will require further observation to determine whether or not this condition is the edematous phase of sclerodactylia.

DR. M. J. REUTER, Milwaukee: I saw a similar picture following acute dermatitis of the hands in a person who had kept the hands immobilized for a long time. Pathologically the condition appears to be a lymphedema. The bilateral character would tend to rule out most neurologic lesions except peripheral neuritis.

DR. H. M. HEDGE: The symptoms have been alternating between blanching and erythema. She noted particularly when she put the hands in cold water, as in cleaning and in performing other activities about the house, that she would have acroasphyxia. The tingling of the fingers was present in the beginning.

A Case for Diagnosis (Pemphigus Erythematodes or Lupus Erythematosus, Bullous Type?). Presented by DR. D. V. OMENS and DR. HAROLD D. OMENS (by invitation).

Mrs. A. G., a Jewish housewife aged 35, presents an inflammatory exudative process of four months' duration involving the upper portion of the cheeks and the lower eyelids. These areas are covered with thick, bulky, friable crusts. Under the crusts is an acute inflammatory weeping surface which dries to form these crusts. The condition begins with slight evidence of bullous formation on a normal skin; the contents of the bullae dry and are soon exfoliated because of the exudative process beneath. There are also lesions on the chest and on the back.

The patient had a gastroenterostomy in 1939, which was followed by a mental disorder developing into a food phobia. She has had fasting periods of two and three weeks at varying intervals. She took sun baths during the summer of 1940. The family history is irrelevant.

A blood count showed 13,500 white blood cells.

DISCUSSION

DR. FRANCIS E. SENEAR: The eruption in this case is one of the borderline conditions that would be classed as bullous lupus erythematosus by some observers. Some have felt that all conditions of this kind are examples of lupus erythematosus with bullous lesions. There are some features which make it compatible with pemphigus erythematodes, provided the eruption is being seen in a much earlier stage than in any other case I have observed. Bullous lesions are developing. She has one near the outer canthus of the right eye today. These subside, leaving a keratotic scale. There has been a certain amount of evanescence. A lesion first developed on the right cheek, which disappeared rather quickly; then the left side became involved and subsequently the right side again. She also has lesions on the chest and on the upper part of the back which are more acute in type than any I have seen in pemphigus erythematodes, but that may be due to the fact that the disease is in the very early stages. I agree with Dr. Ormsby that not all such conditions are lupus erythematosus but that there are examples of pemphigus of the erythematodes variety. In the last patient with that disease I had under observation a typical picture of pemphigus developed, and death followed. In view of the location and course of the individual lesions in this case and their evanescent character, I think the condition might be looked on as early pemphigus erythematodes. I should like to reserve judgment until I have had opportunity to observe the patient longer.

DR. LOUIS A. BRUNSTING, Rochester, Minn: A leukocyte count of over 13,000 per cubic millimeter favors the diagnosis of pemphigus rather than of lupus erythematosus.

DR. MICHAEL H. EBERT: I think the history in this case of some considerable mental trouble perhaps ought to be taken into consideration. I asked the patient whether she had taken any salty medicine or nerve sedative. She undoubtedly has had sedatives. She stated that she had not taken any bromides by name or any medicine which was salty to the taste. I think there is just a possibility of bromoderma in this case. There is something about the condition that does not look like either pemphigus of the erythematous type or lupus erythematosus.

DR. S. W. BECKER: I believe that the most probable diagnosis is pemphigus erythematodes. I should like to give a supplementary report on a patient whose

picture is in Dr. Obermayer's and my text (Modern Dermatology and Syphilology, Philadelphia, J. B. Lippincott Company, 1940, p. 113) and who was presented before this society (ARCH. DERMAT. & SYPH. **39**:918 [May] 1939) with pemphigus erythematodes. Pemphigus vulgaris later developed, and the patient died, with the disease running its usual course.

A Case for Diagnosis (Tuberculous Ulcer?). Presented by DR. MICHAEL H. EBERT and DR. D. V. OMENS.

W. L., a Negro boy aged 13, states that about ten months ago a "bump" developed on the back of the scrotum which itched but caused no pain. There was no history of antecedent trauma. In spite of irregular treatment by his parents and by physicians, the lesion has progressed to become a large confluent ulcer. As an infant he had measles, chickenpox and pneumonia. He does not know of any tuberculosis in the family. He had two sisters who died, but he does not know the cause of death.

Examination reveals a well developed, pale-appearing Negro boy. Midway on the perineum extending to the distal part of the scrotum, on the dorsal surface, in the midline, is an oval deep ulcer with undermining edges and a dirty base. There is an elevation of temperature every afternoon up to 101 F. or less.

The urine was normal. The blood count showed 2,500,000 red blood cells and 10,700 white blood cells, with a differential distribution of polymorphonuclear leukocytes 70 per cent, eosinophils 2 per cent, basophils 1 per cent, lymphocytes 17 per cent and monocytes 10 per cent. There was 58 per cent hemoglobin. The Frei and Ito-Reenstierna tests gave negative results. The reaction to a Mantoux test was positive, and the Kahn reaction was negative. A roentgenogram of the chest showed an increase of the hilar markings on both sides, with calcification in some of the lymph nodes but no active pulmonary disease.

Histologic examination of a specimen from the edge of the ulcer showed a chronic granuloma with several giant cells and epithelioid cells.

DISCUSSION

DR. MARCUS R. CARO: I could not make any more specific diagnosis histologically than a granuloma. I looked for Donovan bodies in the tissue but could not demonstrate them. There are certain features in the section that suggest syphilis, such as plasma cells about the vessel walls, but there are too many polymorphonuclear cells in the infiltrate to be consistent with that diagnosis. I suggest that smears be made and stained for Donovan bodies.

DR. THEODORE CORNBLEET: I should like to see a more intensive examination of the blood to rule out such entities as sickle cell and erythroblastic anemias. Their presence might account for the ulcer. It is true that most of the ulcers associated with these anemias have occurred on the lower extremities, but perhaps other sites, too, could be involved.

DR. CLEVELAND WHITE: Clinically the ulceration resembles closely those chronic undermining, burrowing ulcers due to microaerophilic hemolytic streptococci which Meleny has described so well, though I appreciate the fact that the laboratory studies do not confirm this opinion.

DR. HERBERT RATTNER: The lesion showed little improvement from treatment with sulfanilamide and zinc peroxide. Incidentally, it is my impression that sulfanilamide gives good results in only a few specific cutaneous diseases, such as chancroid, the pyrodermas and erysipelas. The results at the Cook County Hospital usually do not compare favorably with the reports in the literature. I wonder what is the experience of the other members.

DR. S. W. BECKER: I should like to mention the work of Dr. Wiley Sams, of Miami, Fla., with what are called Florida sores. These lesions are impetiginous or ecthymatous and persist for a long time if ammoniated mercury is used. Dr. Sams found that by using sulfathiazole (2-[paraaminobenzenesulfonamido]-

thiazole) in powder or ointment form they could be cleared up quickly. I should like to give a word of warning relative to the use of powders of this kind in large ulcers, however, for they are carcinogenic. Injection of sulfanilamide into mice (Haerem, A. T.: Tissue Response to p-Amino Benzene Sulfonamide [Sulfanilamide] in Mice, *Proc. Soc. Exper. Biol. & Med.* **45**:536, 1940) results in sarcoma in a certain percentage of cases. It is probable that application to superficial lesions would not make much difference. I noted in the literature that wounds have been packed with these powders, but one must be cautious in using large amounts in ulcers.

DR. FRANCIS E. SENEAR: The members present may recall the little girl with severe dermatitis herpetiformis whom I showed last year, who had been treated with various drugs with no result. In the pediatric department at the Research and Education Hospital, University of Illinois, she was given sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and rapidly recovered from the eruption. She had a recurrence, and on administration of the drug the eruption cleared again. I treated another patient with sulfathiazole, a woman who had an extensive bullous dermatitis herpetiformis. It had cleared after she had taken arsenic, but she had had a recurrence. She was readmitted to the hospital two weeks ago and was given 60 grains (4 Gm.) of sulfathiazole a day for two days and then 40 grains (2.5 Gm.) a day for two days, and at the end of that time she was free of the eruption. I do not think that on the basis of these 2 cases one may say that these drugs are going to be curative for dermatitis herpetiformis, but perhaps they will be useful agents when the limit in the amount of arsenic administered has been reached and something else is needed to give the patient temporary comfort.

DR. MICHAEL H. EBERT: I think Dr. Cornbleet's suggestion for a thorough examination of the blood to see whether there is sickle cell anemia is a good one. On the other hand, at present, at least, I feel convinced that this condition is a tuberculous ulcer. As far as looking for Donovan bodies is concerned, in my experience granuloma inguinale is a characteristically proliferating lesion. In this case there is no indication of granulations. The ulcer has overhanging margins and a watery purulent exudate. The type of granuloma seen under the microscope to my mind is tuberculous, but still this has not been proved.

NOTE.—A later examination demonstrated no sickling of the red blood cells.

Keratosis Follicularis (Darier) Treated with Vitamin A. Presented by DR. N. C. BARWASSER (by invitation), Moline, Ill.

W. L., a physician's son aged 38, was presented before the American Academy of Dermatology and Syphilology in December 1940 (ARCH. DERMAT. & SYPH. **43**:1087 [June] 1941).

Intravenous injections of gold sodium thiosulfate, as well as roentgen therapy on selected areas of the body, gave no result. Grenz ray therapy on the medial side of the lower part of the right leg caused a diminution in the lesions of that area.

Administration of vitamin A in doses of approximately 200,000 U. S. P. units per day, by mouth, was begun on Dec. 19, 1940. Within two weeks the horny masses of the leg began to dry, and on removal they left a smooth surface. In six weeks the lesions of the leg had almost entirely disappeared. The lesions on the rest of the body have greatly improved and in some areas have disappeared entirely. The characteristic odor of the disease is absent.

DISCUSSION

DR. LOUIS A. BRUNSTING, Rochester, Minn.: I saw this patient in 1929 and again in December 1940, and the examination today shows that there has been a profound change for the better within the past three months coincident with the administration of large doses of vitamin A. In Darier's disease, as well as in

pityriasis rubra pilaris, there is evidence that the patient is not able to convert the provitamin, carotene, into the final product of vitamin A in sufficient quantities to meet the needs for the regeneration of visual purple in the retina. It is assumed that there is a physiologic block in the liver. It is too much to expect that the disturbance of vitamin A metabolism is the beginning and the end of the pathologic process in these types of dyskeratosis, but the evidence presented in these cases opens an interesting field of research.

DR. A. W. STILLIANS: I am much impressed by the improvement in this patient.

DR. N. C. BARWASSER (by invitation), Moline, Ill.: An interesting observation in this case is that after each of two attacks of pneumonia the lesions cleared somewhat. It was on this basis that the use of hyperthermia was considered, with the hope that repeated fever treatments would bring about involution of the lesions. The mechanism underlying the beneficial effect of fever may be explained by the work of Clausen (*J. Pediat.* **14**:110 [Jan.] 1939) on vitamin A concentration in the plasma. Using a modification of the Price-Carr reaction with antimony trichloride, he found a decrease of vitamin A in the plasma during fever and during infection. He found also that several days after the temperature had returned to normal the amount of vitamin A in the plasma rose above normal and that artificial hyperthermia caused a fall in the vitamin A content of the blood which was followed by a rise above normal. From this I concluded that hyperthermia with administration of vitamin A might hasten involution. However, his work also showed that during infection the ingestion of vitamin A or carotene was not followed by a normal rise of this substance in the blood.

Lichen Urticatus. Presented by DR. FREDERICK R. SCHMIDT.

N. I., a white woman aged 18, presented herself at Grant Hospital on April 16, 1941 for relief of an itching eruption which she has had every summer of her life with one exception. The eruption appears with the onset of warm weather. The present exacerbation appeared three days ago during the first hot days of the year. The skin is entirely clear in the winter.

The skin of the arms, chiefly on the extensor surfaces, is dotted with numerous excoriated papules and pea-sized soft white scars. A few lesions are present on the legs, with scars on the lower part of the back. A fresh lesion appeared during examination of the patient. A pinhead-sized red hard papule suddenly appeared, surrounded by a pinkish blotch about 1 cm. in diameter. The blotch disappeared after one-half hour, leaving the papule. The face is free of papules and scars. No lymphadenopathy was found. Pigmentation and lichenification are absent.

A blood count showed 12,600 white blood cells, with 66 per cent polymorphonuclear leukocytes, 26 per cent lymphocytes and 8 per cent mononuclear leukocytes. The Wassermann reaction of the blood was negative.

DISCUSSION

DR. THEODORE CORNBLEET: An interesting fact is that this patient had a recurrence of the eruption each summer that she lived in the city of New York. Then she moved for one year to live in the outskirts of Flint, Mich., where she was free of cutaneous lesions. She returned to New York, and the eruption recurred the following summer. She finally moved to Flint, Mich., where she was once more free of her eruption. Every one is familiar with the work of the English dermatologists on lichen urticatus, which seems to show that the disease may be due to a sensitivity to dust. At any rate, it was observed that when patients with this disease are transferred to hospitals their eruptions often clear without their receiving any special treatment. I have found the same thing to be true at the Cook County Children's Hospital: the lesions heal spontaneously. I do not know whether the amount of dust in the outskirts of Flint, Mich., is sufficiently less than that in New York city to account for the changed incidence

of lichen urticatus in this patient at these two points. Her mode of living may have been different in the two cities, which would vary the amount of dust accumulation, or there may be some other significant factor.

DR. FREDERICK R. SCHMIDT: Two points of interest appealed to me in this patient's case: first, the definite improvement when she moved to Flint, Mich.—in other words, a change of locality—but, more important, the fact that, as in the present exacerbation, fresh lesions of a dermatosis which has persisted for eighteen years have appeared with each onset of hot weather, yet there has been absolute freedom from lesions during the winter months. The present attack began on Sunday, which was a warm day, after she had been free from the condition during the previous months.

Some months ago a case was presented in which a diagnosis of lichen urticatus was suggested as well as of prurigo, and in the discussion Dr. Ormsby said that in his experience in London in the earlier years he had never seen lichen urticatus develop into prurigo of Hebra. That means a good deal coming from Dr. Ormsby. I think this case bears out that point. After eighteen years there is no lichenification or adenopathy.

BRONX DERMATOLOGICAL SOCIETY

LEO SPIEGEL, M.D., *President*

HENRY SILVER, M.D., *Secretary*

March 27, 1941

Familial Benign Pemphigus (Hailey and Hailey). Presented by DR. CHARLES R REIN.

E. R., a white man aged 50, a broker, born in the United States, was first seen in January 1939 because of an eruption of more than thirty years' duration. His father had had "skin trouble" around the neck for forty-five years and had died at the age of 69 after his gallbladder had ruptured. The patient believes that the eruption was identical with his own condition. His father never sought medical attention and yet had long intervals in which he was free of eruption. The patient has one brother, aged 45, and no sisters. His brother also has a similar eruption of twenty years' duration affecting the neck and both axillas. The brother has received various forms of local and general treatment with little benefit. He has had periods of remission for as long as a year.

The patient has had recurrent attacks of "rheumatism" since 1915. One of the attacks resulted in ankylosis of the left wrist. About thirty years ago there developed an acute gonorrheal urethritis, for which he received immediate treatment. With the exception of the aforementioned diseases the patient has been in excellent general health. His habits are temperate.

The eruption first appeared in the collar area of the neck and was limited to this area for the first twenty years. Ten years ago a similar eruption began to appear in the axillas and groins. The eruption has recurred in these areas at various intervals. He also has had periods of freedom from eruption, lasting at times for one year.

He volunteers the information that any form of local irritation produces a "blister." Occasionally he takes cathartics containing phenolphthalein without altering the eruption.

The eruption consists of discrete and confluent erythematous eczematoid patches. The individual areas are made up of isolated and coalesced vesicles and pustules, most pronounced at the periphery. Many of the vesicles have ruptured and are covered with yellowish brown impetiginous crusts. Some areas show central involution with pigmentation.

At times the Nikolsky sign was elicited on a previously involved area (neck), but it was never possible to produce this phenomenon on sites where the eruption had not been present.

The patient received various ointments, lotions and fractional (75 r) doses of roentgen radiation as well as oral medication, including solution of potassium arsenite U. S. P., calcium gluconate and vitamin therapy. It was observed that two or three fractional doses of roentgen rays produced a rapid involution of the lesions without preventing recurrences. The patient seemed to have responded most favorably to massive doses of vitamins A and D daily. He states, however, that he has had similar periods of remission, either spontaneous or following other forms of therapy.

Urinalysis showed no abnormalities. Examination of the blood showed 4,650,000 red blood cells, 6,600 white blood cells, 100 per cent hemoglobin (Sahli method), 50 per cent polymorphonuclear leukocytes, 41 per cent lymphocytes, 1 per cent eosinophils, 6 per cent monocytes and 2 per cent basophils. The blood sugar determination showed 93 mg. per hundred cubic centimeters of blood. Serologic tests for syphilis, including the Wassermann, Kline and Mazzini tests, gave negative reactions. The Pels-Macht test gave an index of 44 and 43 per cent.

The results of numerous intradermal and patch tests were not significant.

Examination of the lesions on various occasions for fungi in cultures and slides were repeatedly negative. The trichophytin tests gave negative results.

DISCUSSION

DR. ADOLPH ROSTENBERG: I had the opportunity to observe a patient for a number of years who suffered from attacks of recurrent eczema, involving at times either the entire region of the neck or parts of it. It resembled the eruption in Dr. Rein's case, which fits clinically into the picture of a weeping and scaling eczema. I suspected in my case some contact, although I could not establish the offending substance. I fail to see where such a condition fits into the pemphigus group and consider the term pemphigus misleading in such cases. A striking observation in my case, as well as in the case of Dr. Rein, was the fact that the eruption usually cleared after one or two fractional doses of roentgen rays but relapsed in a few weeks. I believe it is far fetched to associate the condition in these cases with pemphigus, and I should rather classify it as a variety of eczematoid dermatitis.

DR. ARTHUR SAYER: By the term benign pemphigus the presenter means an unusual type of this disease, yet the word pemphigus brings to mind a rather serious disease, and the condition in this case is not that. I agree with Dr. Rostenberg concerning the inadequency of the terminology. This man gives a history of taking bromides and salicylates at various times. It seems to me that the condition should therefore be studied from the standpoint of the possibility of a drug eruption. Many bullous lesions are known to be due to the ingestion of drugs. It is necessary that the patient discontinue the use of all drugs for a long time in order to establish the diagnosis.

DR. SAMUEL FELDMAN: Up to recently I could not readily adapt myself to the term benign pemphigus because I had never encountered a case of that description. However, I recall a woman about ten years ago who was treated at the Bronx Hospital, one of a group of 4 patients with pemphigus treated with injections of methylthionine chloride U. S. P. (methylene blue). Three of these died, and 1 was discharged from the hospital improved. She is still alive, but bullous lesions frequently develop just as they did then. The phytopharmacologic index was 64. If there is such an entity as chronic benign pemphigus, the condition in my case is a good example of it.

DR. THEODORE ROSENTHAL: I think this patient's history, the location and the appearance of the lesions are all characteristic of what is thought of as chronic benign pemphigus. In many cases lesions like these have gone on for years. I am thinking of a patient Dr. Chargin and I see occasionally, who has had this con-

dition for at least ten years and whose lesions are located in one area and have not spread. I am ready to accept the diagnosis as chronic benign pemphigus.

DR. DAVID BLOOM: Has the presenter personally convinced himself that the eruption in the other members of the family is identical with that in this patient?

DR. CHARLES A. GREENHOUSE: Any condition that presents bullous lesions with eczematization must in my opinion be regarded as a form of pemphigus. In fact, some modern textbooks describe a condition as pemphigus virginum which does not run the course of pemphigus and occurs in young females. Pemphigus means a bullous eruption. No other confirmatory evidence—not even the Nikolsky sign or the Pels-Macht test—are regarded as diagnostic. Since Dr. Rein has been observing this case for a long period and since these bullous lesions are accompanied by eczematization, one must regard this case as one of benign pemphigus. However, no one could look at the patient for the first time and be convinced that the condition is true pemphigus.

DR. HENRY SILVER: The discussion so far was mainly concerned with terminology. What strikes me as important is the unusual clinical picture and the fact that cases of this type are not encountered frequently. The clinical appearance of the lesions, as seen tonight, does not suggest pemphigus. Dr. Rein, however, states that he has observed bullous lesions. This observation coupled with the presence of the positive Nikolsky sign and the characteristic familial history is sufficient evidence of a unique clinical entity.

The first time that attention was called to this entity was about two years ago by Hailey and Hailey (ARCH. DERMAT. & SYPH. **39**:679 [April] 1939), who labeled it benign familial pemphigus. The histologic sections of their case were studied by Ormsby, who was impressed with the dyskeratosis seen histologically and the discrepancy between the clinical and histologic picture. At his clinic cases of this type were observed. In one family totaling 68 members in three generations, 27 members were affected with the disease, in a mild or severe form. I have the impression that cases like this have been encountered but the condition was not recognized as an entity and was regarded as an atypical form of pemphigus. The condition in the case presented is an excellent example of the type described as bullous dyskeratosis or benign familial pemphigus.

DR. WILBERT SACHS: Different names have been given to this disease. I do not think it belongs to any mentioned. In my opinion it is not a dyskeratosis.

DR. CHARLES R. REIN: Dr. Samuel B. Frank and I had the opportunity to study this patient as well as another patient with the same dermatosis (Frank, S. B., and Rein, C. R.: Dyskeratoid Dermatosis, ARCH. DERMAT. & SYPH., to be published). A number of biopsies were made under varying conditions, and all the specimens from the affected areas presented the same dyskeratoid type of cellular change. Dr. Sachs made a thorough study of the slides and intends to publish independently the histologic observations on this condition. The striking clinical features are a chronic recurrent vesicular or bullous eruption, with definite sites of predilection and occurrence in members of the same family; it can be artificially produced by friction in the areas of predilection, and it responds rapidly and favorably to a few fractional doses of roentgen rays. The predominant histologic feature is a dyskeratosis-like process in the epidermis with formation of epidermic vesicles and bullae.

Lichen Planus et Acuminatus Atrophicans (Feldman). Presented by DR. CHARLES PINES.

V. M., a white woman aged 29, a dressmaker, was seen at the dermatologic clinic of Bellevue Hospital on Feb. 24, 1941. She states that the eruption began about sixteen months previously on the chest. During the last year new lesions have appeared on various parts of the body.

Both sides of the chest and back present papules the size of a pinhead situated about the pilosebaceous follicles. The center of each papule shows a projecting

horny spine. The lesions are grouped, forming patches of various sizes; the majority of those on the chest are red, while others have the color of normal skin. On the left temple, the forehead and the neck and behind the ears there are bluish brown patches with minute horny spines at the follicular orifices giving a nutmeg-grater-like feel on palpation. Subjective sensations are absent. In the occipital region there is a smooth atrophic area the size of a dime.

The tuberculin patch test (Vollmer) gave a positive reaction, which was still positive when seen at the end of sixteen days. The Mantoux test with a dilution of 1:1,000,000 gave a negative reaction and with dilutions of 1:100,000 and 1:10,000 positive reactions. The Wassermann reaction was negative. Roentgenograms of the chest showed healed tuberculosis class III (completely arrested). Histologic examination showed changes strongly suggestive of lichen spinulosus.

DISCUSSION

DR. SAMUEL FELDMAN: I wish the members would dissociate lichen spinulosus from the disease in question. Crocker described lichen spinulosus as an eruptive disease in children. Since then every case of keratosis pilaris or any other follicular reaction with horny plugs is labeled lichen spinulosus. The condition seen in this patient has definite and distinct pathologic changes. On the forehead and temple there are two spinous and pigmented lesions. Lichen spinulosus is not associated with pigmentation, but pigmentation, on the other hand, is a constant finding in the lichen group. Moreover, lichen spinulosus is not even remotely related to the true lichens. This patient has an atrophic lesion on the head which is surrounded by dilated follicles with horny plugs. Graham Little originally described this condition as folliculitis decalvans. In that condition, however, the end process is not an atrophy but scarring caused by pustules, which of course is completely absent in this patient. Histologically all these spinous follicles should show lichen planus changes surrounding them. The well limited round cell infiltration around the follicle extends about three fourths of the distance downward. After describing my first case (ARCH. DERMAT. & SYPH. **5**:102 [Jan.] 1922) I did not encounter many cases, but since the publication of my second paper in 1936 (*ibid.* **34**:378 [Sept.] 1936) I have observed about 20 cases, and it appears that the disease is not as rare as I originally thought. Little's original conception of the disease was erroneous, and he himself recognized that fact, as is shown in his later publications.

DR. MAURICE UMANSKY: The number of reported cases of lichen planus lesions with atrophic areas on the scalp associated with spinous lesions on other parts of the skin has increased lately. Some months ago I presented a similar case which showed lichen planus lesions, proved histologically, and acuminate, follicular lesions. I later discovered areas of atrophy on the scalp in which the hair has fallen out. The occurrence of this combination of symptoms is not a coincidence. Dr. Feldman considers this syndrome a form of atrophic lichen planus. The case presented tonight also shows clinically the three aforementioned elements and belongs to the group of cases observed and described by Dr. Feldman. The finding of lichen planus structure in some of the lesions, at least, is essential to establish the diagnosis.

DR. WILBERT SACHS: The slide shows exactly what Dr. Feldman described, tremendously dilated follicles filled with horny plugs. About each follicle is a simple inflammatory process. I agree with Dr. Feldman that there is neither folliculitis decalvans nor pseudopelade. In the section from the lesion on the scalp one finds the same pathologic structure as in the individual lesions on the body.

DR. HENRY SILVER: This patient presents definite clinical as well as histologic characteristics of the condition described by Dr. Feldman as lichen planus et acuminatus atrophicans, and the disease should be accepted as a clinical entity.

DR. CHARLES PINES: Lichen-spinulosus-like lesions are observed in a number of diseases, such as syphilis, pityriasis rubra pilaris and avitaminosus. In

the case presented they are associated with lichen planus. The patient also presents other clinical features described by Dr. Feldman, and I am, therefore, convinced that this patient's condition is a typical example of lichen planus et acuminatus atrophicans.

A Case for Diagnosis (Scleroderma?). Presented by DR. GEORGE J. SPINNER.

J. R., a white man aged 28, single, is a patient at Fordham Hospital. On the back below the left scapula there is a hard, reddish, infiltrated, sharply marginated, irregular patch, about the size of a child's palm, firmly attached to the skin. There has been no apparent change in the lesion since the onset about four months ago.

The Wassermann reaction was negative. Urinalysis showed no abnormalities. Histologic examination by Dr. L. Ferrara showed stratified squamous epithelium with atrophy of the malpighian layer. The rete pegs were short and stubby and in some places absent. There was only mild keratosis present and some acanthosis. The basal cell layer was intact. In the subepithelial portion there was a definite increase in the collagen fibers so that the tissue appeared dense. Focal accumulation of lymphocytes were seen at regular intervals. The entire cutis was markedly thickened owing to a deposition of a large amount of collagen fibers. Numerous lymphocytes were seen especially around the blood vessels. The collagen fibers were arranged in rather thick bundles and showed intertwining and whirling. Some of the sweat glands and hair follicles were also surrounded by a large number of lymphocytes. The cutis merged into the subcutaneous tissue rather imperceptibly owing to the deposition of collagen fibers. There was slight edema present between the fibrous tissue elements. The blood vessels showed definite thickening and narrowing of the lumen.

DISCUSSION

DR. CHARLES WOLF: My clinical impression is that the lesion represents a lipoid infiltration of the skin.

DR. WILBERT SACHS: Amyloidosis can definitely be ruled out. The process is probably in the fat, or at least in the deep part of the cutis. There is no suggestion of scleroderma, no sclerosis and no fibrosis. There are considerable edema and a marked cellular infiltration, including plasma cells. The section was not taken from a deep enough portion of the tissue; it just reached the involved area. Probably a little deeper in the cutis one would find more characteristic changes.

DR. CHARLES LERNER: Leaving the histologic report out of consideration, the condition does not resemble scleroderma. It is too inflammatory, and the lesion, on palpation, lacks the solidity that one usually finds in scleroderma. The entire patch also gave me the impression of being lobulated or consisting of a group of nodes or masses. I am inclined to consider the condition sarcoid of the Darier-Roussy type.

DR. FRANK CROSS: I suggest paraffinoma; it seems as if some foreign substance were deposited in the skin. Scleroderma can be excluded on clinical grounds.

DR. ARTHUR SAYER: I suggest that this case is one of tertiary syphilis. The presence of plasma cells in the infiltrate favors syphilis rather than Darier-Roussy sarcoid. The histologic picture of Darier-Roussy sarcoid, as is known, shows large groups of epithelioid cells surrounded by connective tissue bands which was not seen in the case reported. I think that a bismuth compound should be administered, and if the effect is rapidly favorable, the syphilitic nature of the lesion will have been proved.

DR. LEO SPIEGEL: About eight years ago I had a similar case under my observation. The lesion was just as large but located a little lower down on the back. Histologic examination showed sarcoid.

DR. SAMUEL FELDMAN: Darier-Roussy sarcoid is almost as unlikely as syphilis. The section does not show any features resembling sarcoid. There is an infiltration of small round cells and plasma cells; it is diffuse and perivascular and reaches nearly to the surface. I cannot offer a diagnosis from the histologic picture.

DR. DAVID BLOOM: I recall the case cited by Dr. Spiegel, which showed the features of the case presented tonight. My diagnosis is Darier-Roussy sarcoid.

Atopic Dermatitis Associated with Lenticular Opacity and Keratoconus. Presented by DR. MARION B. SULZBERGER.

Mrs. C. T., aged 30, had an eczematous eruption at the age of 3 months, for which she was hospitalized. At the age of 15 years she had chronic bronchitis. At that time there developed an eczematous eruption which supposedly appeared after the ingestion of an overdose of potassium iodide, resulting in subsequent hospitalization for three weeks. Her mother had bronchial asthma.

The present eruption has persisted, with exacerbations and remissions. The patient believes that the condition is influenced by eggs, lima beans, white potatoes, dust, silk, wool and feathers. Positive reactions were obtained from tests with several foods and inhalants. In 1930 the patient awoke one morning and was almost completely blind in the left eye. She was operated on at the New York Polyclinic Medical School and Hospital. Several weeks ago she had a similar attack in the right eye.

At present the eruption involves the face, neck, arms and legs (mainly flexural surfaces) and consists of lichenified erythematosquamous excoriated patches. The changes in the lens involve the posterior capsule and the cortical layer. There is a keratoconus in both eyes.

Routine laboratory examinations showed no abnormalities.

DISCUSSION

DR. ADOLPH ROSTENBERG: Did this woman receive roentgen ray treatments? Such ocular changes have been attributed to roentgen therapy.

DR. RUDOLPH L. BAER (by invitation): In answer to Dr. Rostenberg, the patient first received roentgen ray treatments seven years ago, and the ocular complications appeared in the left eye ten years ago and in the right eye six to eight weeks ago.

This case is the second one of atopic dermatitis with cataract which Dr. Sulzberger presented before this society (ARCH. DERMAT. & SYPH. **35**:368 [Feb.] 1937). There seems to be an occasional association between keratoconus and atopic dermatitis, similar to that of certain forms of cataracts and atopic dermatitis.

Localized Scleroderma (Coup de Sabre). Presented by DR. ARTHUR SAYER.

S. M., a housewife aged 36, born in the United States, came to the clinic of Mount Sinai Hospital in the fall of 1940 because of a sharply defined area of baldness on the left side of the scalp, which had developed a few months previously.

The patient presents a bandlike area of alopecia on the left parietal region, about 2½ inches long and ½ inch wide (6.5 by 1.3 cm.), running in a sagittal direction. The skin in this bald area is normal in color, smooth and freely movable. There are slightly elevated ridges forming a border on each side, so that the bald area feels slightly depressed. The scalp shows no seborrhea or other abnormalities. The patient stated that she bumped her head against the kitchen door on several occasions.

Routine laboratory examinations showed no abnormalities. The Wassermann reaction was negative. Histologic examination showed the epidermis to be atrophic and the papillary bodies missing. Immediately below the epidermis there was a circumscribed area of edema. There was only a moderate amount of cellular infiltration. In areas the collagen fibers were sclerotic. These changes corroborate the clinical diagnosis of localized scleroderma.

DISCUSSION

DR. CHARLES WOLF: The lesion is a scar following trauma.

DR. FRANK E. CROSS: This case of scleroderma is an unusual one. I think the smoothness and firmness of the lesion are in favor of this diagnosis. Occasionally one encounters, as in this case, a patch of scleroderma which appears as if glued on.

DR. DAVID BLOOM: I suggest the diagnosis of pseudopelade.

DR. ADOLPH ROSTENBERG: I also incline to the diagnosis of pseudopelade. The lesion is glossy and white, whereas localized scleroderma would be dull white with a slight yellowish tinge.

DR. HENRY SILVER: In my opinion this condition is a typical localized scleroderma of the *coup de sabre* type. The suggestion of pseudopelade can be dismissed, since even the large lesions of pseudopelade seldom reach the size and linear configuration of this lesion.

DR. ARTHUR SAYER: I do not think that the diagnosis of a scar can be seriously entertained, especially in view of the absence of severe trauma to the scalp. I also think that the consideration of alopecia cicatrisata should be eliminated. This configuration would be unusual for pseudopelade, especially, as Dr. Silver pointed out, because of the size and sharp delineation. The affected area has, on palpation, a distinct ridge on either side, which is classic for the *coup de sabre* type of scleroderma.

A Case for Diagnosis (Perforating Folliculitis of the Nose). Presented by DR. CHARLES R. REIN.

E. W., a white man aged 30, presents a small punctate ulceration on the tip of the nose to the right of the midline. The base of the lesion is clean, and the borders appear completely epithelized. The ulceration does not penetrate into the nasal cavity.

The patient states that he first noticed a small pitted lesion in this area about eight months ago and that it has become progressively larger. At present it is more than twice the original size. The patient had applied iodine at one time, after which the lesion became crusted. He has noticed a few hairs extending from the lesion, but at this time the hairs are not seen. On squeezing the nose one is occasionally able to express a small amount of sebaceous material, but it is difficult to determine whether this comes directly from the lesion or from the adjacent sebaceous glands.

DISCUSSION

DR. WILLIAM LEIFER: I believe that the lesion is a basal cell epithelioma. I had a patient, a young man, presenting an almost identical lesion located over the ali nasi. It was a punched-out ulcer, about 4 mm. in diameter, with overhanging edges; the base was grayish and unhealthy in appearance, and there were no granulations and no tendency toward healing. Histologic examination showed basal cell epithelioma.

DR. VAN A. H. CORNELL: The lesion has been present for nine months and is said to have followed the squeezing of a blackhead. Basal cell epitheliomas sometimes develop in such lesions. I thought I discerned a slight rolled border at the edge of the lesion. I believe that the diagnosis is basal cell epithelioma.

DR. ARTHUR SAYER: There is the possibility that the lesion is a sebaceous cyst which has ulcerated through its roof. This type of lesion results from infection of the skin covering the sebaceous cyst. Such a lesion does not heal on the surface but continues to exude a certain amount of sebaceous material, as is seen in this particular case. The only effective method of treatment is destruction or removal of the remaining part of the sebaceous sac. The lesion will then heal by granulation.

DR. CHARLES LERNER: This lesion is a basal cell type of epithelioma despite the youth of the patient. Scalpel excision and suturing would, in my opinion, be the best therapeutic measure. The excised tissue should be studied histologically.

DR. HENRY SILVER: I hesitate to accept the presenter's diagnosis. Perforating folliculitis usually begins at the tip of the nose on the inside and is covered by a dry crust. It is only when the inflammatory process progresses deeper that the lesion reaches the surface and then perforates. The original lesion in this case began on the surface.

Disseminated Xanthomatosis. Presented by DR. MAX B. KAMPF.

A. G., a housewife aged 49, was first seen at the clinic of Fordham Hospital on Feb. 25, 1941. There is no history of diabetes in the family. The eruption began about nine years ago and at that time was confined to the upper and lower eyelids. In 1936 an appendectomy and uterine suspension were performed. Shortly after the operation new lesions made their appearance, first on the extensor surfaces of the elbows and then, in the order mentioned, on the arms, in the axillas, on the under surfaces of both breasts, on the ears, in the postauricular areas and on the neck, the upper part of the chest and the face. The lesions on the face are of approximately ten months' duration. There are also a few lesions on the upper part of the thighs and the buttocks.

The lesions on the eyelids are soft elongated yellowish patches characteristic of xanthelasma. On the face, trunk and extremities the lesions are firm, distinctly yellow nodules varying in size from that of a millet seed to that of a small pea, the average measuring approximately 0.5 cm. in diameter. Those on the ears have joined into somewhat larger lobulated nodules.

Examination of the blood showed 82 per cent hemoglobin, 4,184,000 red blood cells and 5,900 white blood cells, with 69 per cent polymorphonuclear leukocytes, 29 per cent lymphocytes and 2 per cent monocytes. The Wassermann reaction was doubtful. The Kahn reaction was negative. Chemical examination of the blood showed 74 mg. of sugar, 3.5 mg. of uric acid, 27 mg. of nonprotein nitrogen, 10 mg. of calcium, 4.1 mg. of phosphorus and 170 mg. of cholesterol per hundred cubic centimeters. Urinalysis showed no abnormalities.

Histologic examination showed atrophic changes of the epidermis overlying the small tumor. It was flattened, and almost all the rete pegs were absent. Beginning immediately beneath this layer and extending down for some distance in the cutis was an ill defined small nodular mass consisting of numbers of large foam cells, held together by fibroblasts loosely interwoven with a deposition of peculiar giant cells. These showed the typical appearance of the so-called Touton giant cell, characterized by a central area of homogeneous substance surrounded by a collar of well defined nuclei with a narrow zone of foamy substance. Many of the small cells showed this foamy substance and also contained either a compressed or an oval nucleus. There was a moderate number of lymphocytes throughout, and, in addition, there were spaces present which probably contained cholesteral esters.

DISCUSSION

DR. DAVID BLOOM: It is essential to study this case, particularly in regard to the pituitary gland. This type of xanthomatosis is infrequently associated with diabetes insipidus. The blood cholesterol is usually normal.

DR. CHARLES R. REIN: I suggest a trial of treatment with lipocaic or some other form of fat enzyme for this condition.

DR. MAX B. KAMPF: The clinical appearance, the histologic picture and the normal values for blood sugar and blood cholesterol point to a disseminated type of xanthoma.

Superficial Epithelioma in a Psoriatic Patient. Presented by DR. CHARLES PINES.

M. M., a white laborer aged 54, was seen at the dermatologic clinic of Bellevue Hospital in February 1941. He stated that the eruption began about nine years ago on the upper extremities. It progressed gradually and spread to other parts of the body in the course of years. The patient claims that during the summer

months the eruption clears almost entirely except for one lesion on the posterior part of the chest which appeared about two years ago and has persisted to the present time. The past history is essentially irrelevant, except for the fact that the patient has been taking a preparation of unknown content for a considerable time. It cannot be established whether it was arsenic.

The patient presents typical psoriatic lesions at the usual sites of predilection. On the back there is an erythematous sharply defined lesion the size of a dollar slightly depressed below the surface of the skin; the border of this lesion is irregular, somewhat raised and waxy in appearance. Both palms present punctate keratotic plaques, while on the dorsa of the hands there are a few raised dark brown firm keratoses strongly suggestive of arsenical keratoses.

Laboratory examinations showed no abnormalities.

DISCUSSION

DR. MAX B. KAMPF: I questioned this man carefully as to his occupation. He is a laborer on a railroad. The lesions on the palms do not impress me as being due to arsenic. In my opinion they are of occupational origin.

DR. FRANK E. CROSS: The case is interesting because of the combination of psoriasis with keratosis on the palms and soles, probably due to arsenic, and a lesion on the back, which is undoubtedly a superficial basal cell epithelioma; that too may be the result of ingestion of arsenic. I recall a patient under my care who presented various types of lesions, including arsenical keratosis of the soles and palms. There was a history of ingestion of arsenic many years ago. Associated with these lesions was Bowen's disease of the hip and basal-squamous cell epithelioma, as a result of a broken-down arsenical keratosis, of one palm. Montgomery of the Mayo Clinic reported a series of cases of this type (ARCH. DERMAT. & SYPH. **32**:218 [Aug.] 1935).

DR. CHARLES WOLF: No evidence has been produced to indicate that the lesion on the back is an epithelioma. I suggest that this lesion too is part of the entire picture of psoriasis. There is no arsenical dermatitis or arsenical keratosis.

DR. FRANK E. CROSS: I am confident that the lesion on the back will prove to be a basal cell epithelioma. It has a definite, slightly raised, threadlike border and the deep red color of superficial epithelioma and not the pinkish color of psoriasis.

DR. CHARLES R. REIN: This patient has both psoriasis and benign superficial epithelioma.

DR. CHARLES PINES: There were two points of interest in this case: (1) whether the epithelioma was implanted on an old psoriatic patch and (2) whether arsenic played a role. The patient has ingested a preparation over a long time, and there is reason to suspect that it was arsenic. The type of keratosis present is generally observed in arsenical intoxication. While it is possible that the keratotic lesions developed on the palms as a result of the patient's occupation, this would not account for the lesions on the soles and dorsal aspect of the hands. I am certain that the lesion on the back is superficial epithelioma.

NOTE.—Subsequent histologic examination of the lesion on the back showed superficial epithelioma.

Urticaria Pigmentosa (Adult Type). Presented by DR. FRANK E. CROSS.

H. J., a butcher aged 29, single, born in Hungary, was seen at the clinic of Mount Sinai Hospital the first week in February.

The eruption first appeared five years ago. It consists of generalized macules, most numerous on the trunk. The lesions vary in size from that of a pinhead to that of a pea, are deep brown and when rubbed become elevated and surrounded by a pinkish areola.

The blood count and urine were normal. The Wassermann reaction was negative. Histologic examination showed changes mainly in the upper and middle parts of the cutis, consisting of large cells with marked basophilic stippling of the cytoplasm. The diagnosis was urticaria pigmentosa.

Syphilitic Macular Atrophy. Presented by Dr. Henry Silver.

V. A., a window cleaner aged 36, born in Finland, was presented before this society on March 28, 1940 (Arch. Dermat. & Syph. **42**:983 [Nov.] 1940). The lesions were then in the process of transformation from syphilitic papules into macular atrophic lesions.

About six months after the presentation the remaining syphilitic lesions disappeared under treatment. In the wake of these lesions followed typical atrophic macules. They were especially pronounced in the lines of cleavage of the trunk. Most of the atrophic lesions now show wrinkling and herniation.

DISCUSSION

Dr. William Leifer: The syphilitic lesions were rather large and densely infiltrated papules of the lenticular type. I wonder if this lesion is the type which more commonly leads to macular atrophy.

Dr. Maurice Umansky: The secondary lesions of syphilis disappear, as a rule, without leaving scars or atrophy. In the patient presented one witnessed healing and transformation of the secondary papules to macular atrophic lesions.

Dr. Charles Wolf: The observation of Dr. Leifer that the syphilitic papules on the chest left macular atrophic lesions is not correct. The atrophic macules are present on the lower part of the chest and in the abdominal and lumbar regions. Originally I was of the opinion that the beginning atrophic lesions would vanish completely. I was mistaken.

Dr. Max Berkovsky: I can confirm the observation of Dr. Leifer that the atrophic macules occurred at the sites of the large infiltrated lesions. Not every syphilitic lesion left a macular atrophic spot, but those that are present are definitely at the site of former syphilitic lesions.

Dr. Samuel Feldman: When the patient was presented the first time, there were some places where the lesions had not entirely cleared, and even at that early stage there was evidence of atrophy in these areas. I never saw macular atrophy in any form occur on the face. It usually involves the chest and may extend downward.

Dr. Henry Silver: The case was presented last year as a rare instance of actual transformation of syphilitic lesions into atrophic macules. I pointed out that few observers were fortunate enough to see the various stages of transition of a syphilitic papule to the end stage of an atrophic macule. It was not difficult to predict that in a few months the patient would present the fully developed picture of macular atrophy. Tonight there is no question that all lesions are typical atrophic macules. The atrophy has many characteristics of the type described as anetoderma of Schweninger and Buzzi.

BROOKLYN DERMATOLOGICAL SOCIETY

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April 21, 1941

Dermatitis Medicamentosa (Fixed Arsphenamine Eruption). Presented by Dr. A. Walzer.

N. D., a man aged 22, is presented for Dr. A. Blau from the Social Hygiene Clinic of the Department of Health, where he was being treated for syphilis with alternating courses of bismuth and old arsphenamine therapy. He received the first injection of arsphenamine in December 1939. No cutaneous manifestations were noted after this course, which was completed in February 1940. Another course of arsphenamine therapy was started on June 7, 1940. The eruption was

first noted about Aug. 9, 1940, after the fifth injection of the second course. The third course was started on March 21, 1941, and the eruption has been recurring after each injection.

Neoarsphenamine, 0.3 Gm., was given this morning. The patient stated that it took seven hours for the eruption to flare up.

The eruption consists of about a dozen dark brown, pigmented, slightly raised, coin-sized patches, of variable sizes and indefinite outlines and is on the left wrist, the back of the neck, the abdomen, the buttocks and the thighs.

The Wassermann reaction of the blood on numerous occasions was 4 plus. The Wassermann reaction of the spinal fluid was positive.

DISCUSSION

DR. A. BLAU (by invitation): All the previous injections of neoarsphenamine did not give the reaction that he got from the old arsphenamine. At the beginning of the course of arsphenamine therapy he did not have any eruption, but when the middle of the second course was reached the rash occurred after every injection. The reaction is not as pronounced now as it has been.

DR. M. L. WEITZ: It would be interesting to see in this patient the effects of mapharsen, that is, to see whether or not a similar eruption would develop after an injection of mapharsen. I do not think there is any question that this condition is a drug eruption due to sensitivity to arsenic.

DR. LOUIS CHARGIN: Most of you are acquainted with a paper Dr. Leifer and I recently published (*J. Invest. Dermat.* **3**:443, 1940). We had extensive experience with this type of eruption and reported 65 cases. Mapharsen does not cause as many reactions as the other arsenicals. In considering this type of eruption two points should be borne in mind: (1) that this drug never leads to a serious type of arsenical eruption, and (2) that frequently there is a tendency for lesions to appear on the face. The second statement is an important consideration, because the eruption may last for some time. I can recall 1 case in which the eruption lasted for more than five years. If the patient has early syphilis and a sensitivity to one of the arsenicals, one should progressively try the other arsenicals and hope that one or another will not produce an eruption, so that the syphilis therapy may be continued.

Dermatitis Medicamentosa (Phenolphthalein?). Presented by DR. JOEL SCHWEIG.

S. P., an Italian aged 55, a married laborer, had been well up to the time this eruption appeared, about six weeks ago. The eruption appeared at first on his chest, spreading within a few days to other parts of the body, the lesions increasing gradually in size, causing severe itching, as evidenced by numerous excoriations. He had no medication of any kind prior to the eruption. He did not take laxatives or sedatives. The Wassermann reaction of the blood was negative; his blood count showed 4,200,000 red blood cells and 10,800 leukocytes, with 75 per cent neutrophils, 17 per cent lymphocytes, 4 per cent monocytes and 4 per cent eosinophils. Examination of the urine disclosed no abnormalities.

The eruption involves practically the entire body with the exception of the face, palms and feet. It predominates on the trunk and involves the extremities to a much lesser degree. It consists of sharply defined, round, dark red plaques, indurated more at the margins. The surface of the lesion is colored with dark gray adherent scales. The plaques on the chest, buttocks and flanks have merged into large infiltrated areas, forming polycyclic configurations. There is no decided adenopathy.

Applications of bland ointments caused the eruption to undergo involution within six weeks, leaving deeply pigmented areas on the sites of previous lesions.

DISCUSSION

DR. JOEL SCHWEIG: The patient presents today the terminal stage of the dermatosis. When I first saw him at the clinic about eight weeks ago, the

consensus was that the condition was a lymphoblastoma. I was much surprised that after several weeks of application of boric acid ointment the plaques showed quick resolution, leaving the deeply pigmented areas as seen today.

DR. LOUIS CHARGIN: My impression of the condition in this case is that it is a fixed eruption of some type. I do not think I would label it as due to phenolphthalein, for it might be due to antipyrine or to other drugs.

DR. ABRAHAM WALZER: Polyvalent sensitivity is not by any means rare. In other words, a patient sensitive to one drug may eventually become sensitive to others. However, nonspecific reactions with other drugs or foods must also be considered. For example, a patient sensitive to fish gets a reaction after the ingestion of this fish. As the rash is subsiding, or right after the rash has disappeared, the patient takes acetylsalicylic acid and the rash may recur. On the other hand, if that patient should take the same drug a week or so after the rash had disappeared, no reaction would follow. In other words, the reaction after the ingestion of acetylsalicylic acid was a nonspecific reaction and did not indicate a definite sensitivity to the drug. The same thing applies to contact dermatosis. A rash due to contact to a cold cream might be reproduced at the time the rash had about disappeared by the use of soap and water. The patient, however, could use soap and water freely a short time after the rash had disappeared.

DR. JOEL SCHWEIG: I agree that what impressed me as infiltration must have been nothing but edema. This can be said only in retrospect and could not have been decided clinically at the time the patient was first seen. I concede that the eruption may have been caused also by antipyrine or the barbiturates. Phenolphthalein may be ingested also in other forms than in laxatives, such as in ice cream, cake icings and candies.

A Case for Diagnosis (Eczema Venenatum). Presented by DR. SEYMOUR H. SILVERS.

Mrs. M. B., a white woman aged 33, mother of one child, was admitted two months ago to the dermatologic department of Wyckoff Heights Hospital, complaining of an itchy eruption of the face of four weeks' duration, which became worse in the evening. When she was first seen, she showed an acute vesicular, papular, oozing, crusted eruption of the face, most evident around the eyes and mouth. She used "mange cure" to wash her hair and numerous cosmetics, nail polish and nail polish remover but not mascara.

Examination now shows a fairly well defined eruption of the eyelids and extending around the eyes, of fawn-colored redness with edema and thickening. There is also an ill defined area of redness and scaling around the mouth.

Patch tests performed with her cosmetics, nail polish, nail polish remover and facial soap all gave negative reactions. A patch test with mange cure elicited a positive reaction, consisting of papules and scaling, in forty-eight hours.

DISCUSSION

DR. SEYMOUR H. SILVERS: I believe that a case was recently reported (ARCH. DERMAT. & SYPH. **42**:218 [July] 1940) of an eruption about the eyes due to nail polish. This patient could not remember whether the eruption followed her use of the "mange cure." The eruption persisted for two months. She does not use soap and water; she was given only bland ointments. She never had an eruption on the forehead, where the substance she used would normally make the first contact; the eruption was mainly around the eyes and mouth. Tonight she shows edema with a peculiar yellowish color and an ill defined patch on the side of the face.

DR. JACOB SKEER: I agree with the diagnosis. I think the condition is a form of dermatitis due to some external irritation but could not find out just what. I questioned her on nail polish and hair tonic. She also uses brilliantine. She has a peculiar hue which one sometimes sees in carotenemia.

DR. IRVING N. HOLTZMAN (by invitation): There has been a great increase of nail polish dermatitis in the literature. One of the first reports was by Hollander (*J. A. M. A.* **115**:1714 [Nov. 16] 1940); in 2 cases patch tests did not give positive reactions but the condition cleared up after application of the nail polish was discontinued. The dermatitis almost invariably clears up after the use of nail polish is stopped.

DR. L. M. FRUCHTBAUM: This woman is a prodigious reader of newspapers, and there is a possibility that while reading the rotogravure section of the paper she rubbed her eyes, causing the onset of her cutaneous condition.

DR. H. L. FEIGENBAUM: In the article by Dr. Hollander it was reported that several patients did not show a reaction to patch tests with nail polish, yet when the nail polish was removed the lesions cleared up. As far as the diagnosis is concerned, it seems clear that if the patient is sensitive to "mange cure" she should not use it. However, the distribution of the eruption may be due to the structure of the skin, which is more delicate around the eyelids than around the scalp.

DR. LOUIS CHARGIN: In my own practice I had a patient who had been seen by other dermatologists and who had given negative reactions to patch tests with nail polish. When I saw her I asked her to leave off the nail polish for four weeks; later she reported to me and she was well. Nail polish must be removed, as it is usually the offending agent. As a rule, the upper eyelids are involved, seldom the lower lids.

DR. SEYMOUR H. SILVERS: Carotenemia is not an inflammatory disease. It is simply a deposit of carotene in the skin. Certain areas may have a predilection for carotene, such as those where there are numerous sebaceous glands and where the horny layer of the skin is thickest.

Lupus Erythematosus (Lupus Pernio). Presented by DR. L. M. FRUCHTBAUM.

V. F., a woman aged 27, complains of a red patch on the bridge of the nose and on the cheeks of six months' duration. It began with a small red spot on the nose and gradually spread to the sides of the nose and to both cheeks. There were fine telangiectases on both cheeks.

During the past four months she has received twelve intramuscular injections of bismuth subsalicylate, 2 grains (0.13 Gm.) each. The patch on the nose has become much lighter, and the redness of the cheeks disappeared entirely except for the telangiectatic streaks. The patient returned one week ago, at which time the patch on the nose was a mixture of blue, red and brown; the surface of the lesion was rough to touch; the tip of the nose looked pale and gave the impression of atrophied skin, and new patches covered with scales appeared at the nasolabial folds. The redness of the cheeks was also more prominent.

The serologic tests for syphilis gave negative results.

DISCUSSION

DR. L. M. FRUCHTBAUM: There are two types of pernio. One is the tuberculous type of Besnier, and the other is the lupus erythematosus of Hutchinson. There is a difference in clinical as well as in histologic appearance. In the latter there are no tubercles, whereas in the former there are. The distribution is different. Because of its distribution, location and appearance, I think the condition in this case is lupus erythematosus of the pernio type.

DR. A. WALZER: This condition is lupus erythematosus and has nothing to do with pernio.

DR. C. T. CHIARAMONTE: I agree that this patient has all the characteristics, including follicular keratotic plugging, but I find it difficult to account for the discoloration of the lesion. The brownish discoloration, I thought, was unusual for lupus erythematosus.

MINNESOTA DERMATOLOGICAL SOCIETY

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Minneapolis, May 2, 1941

A Case for Diagnosis (Mycosis Fungoides d'Emblée?). Presented by DR. S. E. SWEITZER, Minneapolis.

Mrs. B. P., aged 54, white, had phlebitis of the left leg after a delivery thirty years ago. After that the left leg was somewhat larger than the right and always caused some pain. Ten years ago masses developed in the left calf and disappeared after six weeks of rest in bed. Two and one-half years ago these masses recurred and persisted in spite of treatment. One and one-half years ago ulceration occurred in a pigmented area 1 cm. in diameter. This ulceration progressed in spite of all treatment, and she entered the Minneapolis General Hospital the last of March 1940. Examination then showed an ulcer covering most of the middle third of the left calf and extending three fourths of the way around it. The ulcer varied in depth from 0.5 to 5 cm. The border was precipitous and surrounded by an erythematous halo. The floor of the ulcer was covered by pink granulation tissue. Histologic examination of the border of the ulcer and floor showed nonspecific chronic granulation tissue. The ulcer failed to heal with local therapy, and in September the leg had to be amputated below the knee because of toxic absorption. The patient made an uneventful recovery and was discharged from the hospital.

Two months ago she again returned with multiple painless subcutaneous nodules on the stump of the amputated leg, on the right thigh, in the right popliteal fossa and over the right scapula. Several lesions subsequently became dusky red and ulcerated. Many new nodules have appeared in the past two weeks.

The Wassermann, Kahn and Kline tests gave negative reactions. Specimens from the amputated leg, from the lesion on the back and from the excised nodule were examined histologically. A roentgenogram of the chest was normal. A blood count showed 4,500,000 red blood cells and 3,500 white blood cells, with a differential count of 63.5 per cent polymorphonuclear leukocytes, 19.5 per cent lymphocytes, 12 per cent monocytes and 5 per cent eosinophils; the hemoglobin amounted to 84 per cent.

DISCUSSION

DR. CARL W. LAYMON, Minneapolis: I think the condition is some form of lymphoblastoma. It seems extremely difficult to differentiate between mycosis fungoides of the d'emblée type and leukemia. The clinical features fit leukemia better, while the histologic changes favor a diagnosis of mycosis fungoides. Further observation will be necessary to make a decision.

DR. E. A. STRAKOSCH (by invitation), Minneapolis: When I first saw the microscopic section from the lesion on the back, I suggested the diagnosis of mycosis fungoides d'emblée. I showed the sections to Dr. E. T. Bell, who stated the belief that the diagnosis mycosis fungoides is the most probable one. In going back over the history, I believe it is probable that the original nodule on the left leg, which finally broke down, was the starting point of her ulcer and was analogous to the present ones. I also showed to Dr. Bell the histologic sections from the amputated leg, and he stated that the infiltrate in some places was suggestive of mycosis fungoides.

DR. L. H. WINER, Minneapolis: This patient has had four different biopsies: The first and second showed chronic granulation tissue and ulceration; the third, of a specimen from an ulcerating lesion over the right scapula, suggested mycosis fungoides because of the preponderance of lymphoid-like cells which contained round dark nuclei and broad cytoplasmic borders; in addition, the infiltrate con-

sisted of eosinophils, lymphocytes and fibroblasts; the fourth biopsy, of a specimen taken from a tumor of the left leg, showed an infiltrate of multiform cells, consisting of lymphoblasts, fibroblasts, eosinophils and large monocytes, and also large multinucleated cells. From a consideration of the clinical course and the histologic sections I agree with the diagnosis of mycosis fungoides.

Spindle Cell Sarcoma of the Leg. Presented by DR. S. E. SWEITZER, Minneapolis.

A. P., a white man aged 59, stated that about one year ago a small growth appeared on the calf of the left leg, which gradually enlarged and bled occasionally. About three weeks ago he noted numerous maggots in and about the tumor.

Examination shows a large necrotic new growth measuring 20 by 12 by 9 cm. on the left leg. Numerous maggots and eggs were present. A roentgenogram of the leg showed no involvement of the bone. The hemoglobin value was 16 per cent.

The microscopic examination showed spindle cell sarcoma.

DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis: Sarcomas of the skin are extremely rare, and it has always been taught that in any odd tumor sarcoma should be considered as a possibility. This patient is decidedly below the normal in his mental reactions, and I doubt if he is at all concerned about the lesion.

DR. L. H. WINER, Minneapolis: This large, soft, flabby, nodular tumor with its hemorrhagic areas did not suggest sarcoma to me clinically, but the histologic picture definitely indicates spindle cell sarcoma.

Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi. Presented by DR. L. H. WINER, Minneapolis.

J. C., a white man aged 46, complains of lesions on the lateral and medial sides of the feet and on the ulnar sides of the hands. The lesions began on the inner surface of the right foot five years ago and subsequently appeared in the other locations. Four years ago the patient had a bleeding tumor on the inner surface of the right foot. There was also a bleeding tumor on the right ear. Both of these lesions were cauterized by a physician. The individual lesions have been growing peripherally. They itch on rare occasions.

Examination shows bluish red irregular plaquelike areas from ½ to 2 inches (1.3 to 5 cm.) in diameter on the inner and outer surface of the ankles and on both soles. Similar sharply bordered areas are present on the ulnar sides of the hands. The skin of the lesions on the hands did not appear as infiltrated as did that of the feet. The dorsa of the toes and of the feet are bluish red. The color can be expressed from all lesions on pressure.

(Histologic sections were shown.)

DISCUSSION

DR. L. H. WINER, Minneapolis: Histologic examination of specimens taken from the lesions of the hand and foot showed vascular dilatation and a nonspecific cellular infiltrate which in places is uniformly fibroblastic. There was no extravasated blood present. He has had 330 r of roentgen rays filtered by 1 mm. of aluminum in the past seven days.

DR. H. E. MICHELSON, Minneapolis: I think Dr. Winer has made a good diagnosis, but the case will require longer observation before one can be completely certain.

Lichen Spinulosus. Presented by DR. S. E. SWEITZER, Minneapolis.

M. K., a white woman aged 21, was admitted to the Minneapolis General Hospital on Nov. 19, 1940 with a rash on her body of four months' duration.

When first noted the lesions were "spots" on the left shoulder; later they appeared on the chest, thighs, legs and arms. There was no itching. On admission the eruption consisted of red oval macules the centers of which showed branny scales. The diagnosis of pityriasis rosea was made, and the patient was treated with half-strength compound ointment of benzoic acid N. F. and ultraviolet irradiation. The lesions became eczematoid, and the patient was treated with 1 per cent coal tar in paste of zinc oxide. She was discharged from the hospital on December 3, at which time her eruption was decidedly improved.

Three weeks later she reported to the outpatient department with a follicular hyperkeratosis on her body. She was treated with injections of 20,000 U. S. P. units of vitamin A daily for eight weeks and then every second day, without any improvement. The photometric examination for night blindness gave normal results.

The eruption consists of follicular hyperkeratosis and plugging in irregular areas, some the size of the palm and some larger. There is no line of demarcation. The areas involved are the shoulder, back, chest, abdomen and thighs.

The reaction to a Wassermann test was negative, and the results of all other laboratory tests were normal.

(Histologic sections were shown.)

DISCUSSION

DR. CARL W. LAYMON, Minneapolis: The histologic picture in this case suggests lichen planus. There were also retiform lesions in the mouth which could have been lichen planus. In cases of follicular hyperkeratosis due to a lack of vitamin A many weeks or months of vitamin A therapy are required for a therapeutic result.

A Case for Diagnosis (Lichen Planus)? Presented by DR. S. E. SWEITZER, Minneapolis.

S. K., a white man aged 84, first noted round pigmented lesions on both lower extremities many years ago. There was never any itching. He was recently hospitalized for the treatment of gout. Examination shows on both lower extremities an eruption consisting of depressed violaceous to brown angular lesions covered by a firmly attached grayish mottled scale. The lesions vary in size from 0.3 to 1 cm. in diameter. The largest are on the calves, in which areas the scales are most firmly attached. There seems to be no tendency toward confluence of the individual papules.

(Histologic sections were shown.)

DISCUSSION

DR. E. A. STRAKOSCH (by invitation), Minneapolis: I did not think that the microscopic picture could be brought in line with a diagnosis of lichen planus.

DR. L. H. WINER, Minneapolis: The microscopic features of lichen planus are not always fixed. The microscopic picture in this case appears more like that of atrophic lichen planus than that of active lichen planus. The epidermis was atrophic; the basal cells were degenerated, and the upper part of the cutis appeared washed out and edematous. The clinical appearance together with the histologic picture allow the diagnosis of lichen planus atrophicus.

DR. D. D. TURNACLIFF, Minneapolis: I do not recall having seen extensive old lichen planus of the lower parts of the legs which was not hypertrophic.

Xanthomatosis with Myxedema. Presented by DR. S. E. SWEITZER and DR. L. H. WINER, Minneapolis.

This patient, previously described (ARCH. DERMAT. & SYPH. **42**:419 [Sept.] 1940), now shows complete resolution of the xanthomas from the administration of thyroid, 1½ grains (0.1 Gm.) daily, which she is still taking. Her present basal metabolic rate is —7 per cent.

Lupus Erythematosus. Presented by DR. FRANCIS W. LYNCH, St. Paul.

L. W. has previously been presented on numerous occasions (unpublished). He is now shown after treatment with a high fat diet (carbohydrates 80 Gm., proteins 75 Gm. and fat 150 Gm.). The cholesterol level in the blood has remained constant at about 240 mg. per hundred cubic centimeters after twelve days on the diet. There is improvement in the eruption.

DISCUSSION

DR. F. W. LYNCH, St. Paul: This patient undoubtedly shows improvement after hospitalization and institution of a diet high in fat, though it is not possible to state that the diet is the cause of the improvement. This treatment is being tried because of an experience with another patient who had suffered from lupus erythematosus constantly for fourteen years. In September 1940 he returned to my office with hundreds of xanthomatous papules, a loss of 40 pounds (18 Kg.) in weight and other symptoms of diabetes mellitus; the lupus erythematosus had nearly disappeared. After a proper diabetic regimen, the patient regained 10 pounds (4.5 Kg.); the serum cholesterol returned to normal, and the xanthomas disappeared. The lupus erythematosus returned to the extent present before the onset of his diabetes. It is because of these observations that I have recently treated lupus erythematosus by diet. In the patient presented tonight the intravenous administration of dextrose will be tried later.

Ariboflavinosis (Avitaminosis). Presented by DR. H. E. MICHELSON, Minneapolis.

Mrs. A. V., a white woman aged 40, noted sore tongue and mouth four months ago. An eruption also appeared on the central part of the face about the same time. For about five months she has had a poor appetite and weakness for unknown reasons. For breakfast she usually had a piece of toast, an egg and a cup of coffee. She ate no lunch, and her dinner was usually composed of a small portion of vegetable, a slice of bread, fruit sauce and a glass of buttermilk.

After one week's treatment with riboflavin (1 mg. four times a day), the tongue and mouth are no longer sore; the facial eruption has almost disappeared, and the appetite has increased enormously.

DISCUSSION

DR. CARL W. LAYMON, Minneapolis: This patient was referred to the dermatologic clinic from the medical clinic, where she had been receiving treatment with a gold compound for arthritis. She had lost considerable weight and had no appetite. When I first saw her she had a sore red tongue and a seborrheic-like eruption on the central part of the face. It is interesting to note that in Ceylon similar lesions have been observed in patients whose diets were rich in riboflavin. This fact led observers to believe that in certain foods there are chemicals which inhibit the activities of riboflavin or prevent its utilization.

DR. H. E. MICHELSON, Minneapolis: One must realize that various drugs influence the utilization of vitamins. The gold compound injected may have played such a role in this case.

Pachyonychia Congenita (Jadassohn). Presented by DR. H. E. MICHELSON, Minneapolis.

P. K., a 2 year old white girl, was first seen in the dermatologic outpatient department in March 1941. At that time the patient's mother stated that the finger nails and toe nails had been deformed since birth and that lesions had been present on the knees and elbows for three months. Blisters developed on the

child's feet when she started walking, but these have largely disappeared. There was no family history of disease of the nails or skin.

All the nails of the fingers and toes are thickened, dry, brittle and brown. On the knees and elbows are multiple, tiny, follicular, hyperkeratotic papules. The tongue and the cheeks are covered with white leukoplakic patches. The hair appears normal.

DISCUSSION

DR. C. W. LAYMON, Minneapolis: There are three types of this disease: one in which there are nail changes along with follicular hyperkeratotic papules; a second type in which there are leukoplakic plaques in the mouth in addition to the other features, and a third type in which there is involvement of the conjunctiva. It would be interesting to try large doses of vitamin A in this case. I felt that the bullae on the feet were due to pressure, since they appeared after the child had worn a new pair of shoes.

Necrobiosis Lipoidica Diabeticorum. Presented by DR. H. E. MICHELSON, Minneapolis.

Mrs. A. G., aged 59, white, was told two years ago that she might have diabetes. She came to the University Hospitals April 29, 1941, at which time her fasting blood sugar was 211 mg. per hundred cubic centimeters. She first noted lesions on the legs three years ago. Lesions over both tibial surfaces came directly following bruises. Since then the lesions have increased gradually in size and number.

The lesions are located on the anterior surfaces of the legs below the knees. All are similar except for size. The smooth surface, the orange-yellow centers and the atrophy coincide with the diagnosis of necrobiosis lipoidica diabeticorum.

DISCUSSION

DR. C. W. LAYMON, Minneapolis: One interesting feature of this case is that the patient had received injections for varicose veins; the physician stated the belief that the eruption represented stasis dermatitis. Dr. Sweitzer and I have noted the same thing in cases of acrodermatitis chronica atrophicans. In neither condition should such a procedure be undertaken.

Book Reviews

Photodynamic Action and Diseases Caused by Light. By Harold Francis Blum, Ph.D., American Chemical Society Monograph Series, No. 85. Price, $6.00, cloth. Pp. 309, with 50 illustrations. New York: Reinhold Publishing Corporation, 1941.

In spite of a considerable amount of fundamental research on the problem since the turn of the century, the subject of photosensitivity remains a challenging portion of the unknown in dermatology. This book is a treatise on two parts of this field, photodynamic action and diseases caused by light. The author, as a biophysicist and a physiologist, analyzes the relation between the two and points out how basic principles in physics and in photochemistry may be employed profitably to establish a rational system of classification of these diseases in animals and in man.

The volume consists of four parts and has a total of twenty-four chapters. It is planned that each section of the book may be read independently of the others, although a knowledge of fundamentals is essential to the understanding of the whole. This is comforting to the clinician, who in part 1 is confronted with a formidable array of tables, charts, formulas and discussions of spectrums in connection with a review of the elementary principles of light and radiation in general and a discussion of their biologic effects. Part 2 is a thesis on photodynamic action and its similarity to photosensitized oxidations in living systems. In this section the discussion of conditioning factors and alternative hypotheses becomes rather involved. The second half of the book deals with clinical phases of photosensitivity. Part 3 concerns diseases caused by light in domestic animals following the ingestion of noxious weeds and buckwheat. Certain important conditions of sheep and cattle—hypericism, geeldikkop and fagopyrism—are presented in detail, not only to emphasize their economic significance to veterinarians and stockmen but to show experimentally that in all likelihood the mechanism of sensitivity in these conditions is based on photodynamic action. In the discussion, in part 4, of diseases in man caused by light the author demonstrates a wide acquaintance with the problems of the dermatologist in this clinical field. He proposes a classification on the basis of the particular spectral fractions which provoke a characteristic eruption in irradiated skin. In the elaboration of the technic of the experimental approach it becomes clear why it is not feasible at present to formulate a standard procedure of testing for sensitivity to light. In the text primary divisions, such as urticaria solaris, polymorphic light eruptions and hydroa, are discussed at length, and there is an excellent review of the role of porphyrins in photosensitivity. The subject of the influence of light on such borderline conditions as pellagra, lupus erythematosus and cancer of the skin is presented in the concluding chapters.

Throughout the volume the historical development of the subject, the voluminous bibliography and the author's personal contributions are well handled and appropriately distributed. This book admirably serves the purpose of the sponsors: it reviews the chosen topics; it links a clinical problem with a basic science, and it points out the direction in which research needs to be extended. For the practitioner it is an excellent work of reference; for the dermatologist it is a text, and for candidates for certification in dermatology it should be required reading.

Congenital Syphilis. By Charles C. Dennie, M.D., and Sidney F. Pakula, M.D. Price, $8.00. Pp. 596. Philadelphia: Lea & Febiger, 1940.

If congenital syphilis is ever to be eradicated it will be done only through the combined effort of members of several branches of medicine, including internists, obstetricians, pediatricians and general practitioners, as well as dermatologists. This volume is of particular value because it points out the part each specialty can play in the elimination of this disease.

The book is divided into twenty logical chapters which discuss the examination of the syphilitic infant, serologic reactions (in which a splendid approach is made to the problem of "syphilotoxemia") and syphilis of pregnancy and separate chapters describing congenital syphilis as it affects the eyes, bones and joints, the central nervous system and the viscera. It is properly pointed out that with modern methods of diagnosis and treatment no woman should bear a syphilitic baby.

The problem of uncovering latent congenital syphilis is dealt with in a thorough manner. The reviewer agrees enthusiastically with the value of slit lamp examinations in the disclosure of latent congenital syphilis. The moot question of third generation syphilis is discussed. The authors describe their own series of cases: 22 syphilitic persons born in fourteen families in which the mother was herself congenitally syphilitic. Without any attempt on the reviewer's part to be too critical, it seems that there is more than a remote possibility that some of these patients might have been conceived of mothers who had been superinfected with acquired syphilis.

A large portion of the volume is devoted to various forms of therapy. A critical appraisal of the different chemical agents is made, and their indications and contraindications are set forth. In discussing mapharsen, the authors state that Herxheimer reactions with this drug are rare. This statement does not agree with the experience of others. In addition to chemical agents, much space is properly used in carefully describing the various means of hyperpyrexia. Many of the suggestions made for the proper management of therapeutic malaria are valuable.

There are a generous number of worth while photographic illustrations; for the most part these are clear halftones showing what is expected of them. The paper is of satisfactory quality; the binding is substantial, and the general setup of the book is pleasing.

This splendid book dealing with an important field of medicine is recommended to students, general practitioners and specialists.

Diseases of the Nails. By V. Pardo-Castello, M.D. Second edition. Price, $3.50. Pp. 173, with 98 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This well known and widely read monograph is now presented in its second edition by the author, who is a recognized authority on this subject. In this edition new therapeutic principles have been added, as well as new illustrations and mention of many recent additions to the literature. The illustrations are of excellent quality and definitive. The book is set in large type, which allows easy reading.

For the sake of convenience and for purposes of classification the subject matter is divided into four chapters: conditions peculiar to the nails, onychodystrophies, ungual manifestations of dermatoses and systemic diseases and congenital conditions of the nails.

All known common and rare conditions of the nails are discussed and accurately described. Suggestions for treatment are simplified and are limited to those procedures which have been proved effective. There is a long list of occupations that are known to produce changes in the nails, including the symptoms and the causative agents. The bibliography is extensive and affords an excellent source of references to the literature on this subject. Also, histologic and pathologic changes in nails are described.

As current standard textbooks on dermatology contain only brief and incomplete accounts on diseases of the nails, there is a definite need for a monograph of this type. The information assembled in this book will afford an invaluable aid in the diagnosis and treatment of disease of the nails.

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